The American Journal of Medicine





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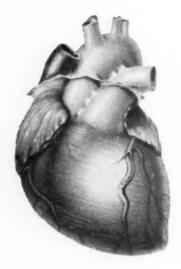
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REFERENCES

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Editorial

Genetics, Hypersensitivity and the Connective Tissue Diseases . . . Morris Ziff

Clinical Studies

Postural Natriuresis and Urine Osmotic Concentration in Hydropenic Subjects
WILLIAM H. HULET AND HOMER W. SMITH 8

An examination of the significance of the phenomenon, long known, of the transient increase in urine flow when human subjects change from the erect to the recumbent position. The diuresis could readily be shown to be due primarily to a natriuresis but the puzzling finding was that the osmotic concentration of the urine remained constant throughout the diuresis. This would imply some form of self regulation of the transport of sodium from the loop of Henle to the medullary interstitium. The nature of such a regulatory mechanism is subjected to searching scrutiny in an informative analysis of the various factors which might come into play. It is concluded that sodium transport in the loop of Henle is self-limited by a maximal sodium concentration in the interstitium or, more likely under the circumstances of postural diuresis, by the concentration gradient between the medullary interstitium and the urine in the loop of Henle.

Hemodynamics of Idiopathic Orthostatic Hypotension

Albert G. Bickelmann, Eugene J. Lippschutz and Carl F. Brunjes 25

Two cases of orthostatic hypotension are presented, with studies of arterial pressure and cardiac output on recumbency and tilting. With tilting there was a sharp fall in cardiac output, due primarily to venous pooling and defects in venomotor tone. There was also a marked fall in arterial pressure, reflecting failure of normal reflex vasopressor changes. The physiologic and therapeutic implications are discussed informatively.

Circulating Antihuman Kidney Antibodies in Human Renal Disease

NORMAN C. KRAMER, MARY F. WATT, JOHN H. HOWE AND ALVIN E. PARRISH 39

In this interesting study latex particles were coated with human kidney antigen and then exposed to the serums of diseased and normal human subjects in order to detect the presence of circulating antihuman kidney antibody. This agglutination test proved to be more specific than previous such tests, being positive only in patients with glomerulonephritis, although only in fifteen of thirty-six tested. The results support the thesis that renal autoantibodies are formed in glomerulonephritis and may play an important role in pathogenesis.

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REFERENCES

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Hypothalamic-Pituitary Sarcoidosis. A Report on Four Patients, One with Prolonged Remission of Diabetes Insipidus Following Steroid Therapy

C. NORMAN SHEALY, LAWRENCE KAHANA, FRANK L. ENGEL AND HARRY T. McPherson

An informative discussion of sarcoid granulomatous involvement of the hypothalamus and/or pituitary gland, with an account of four presumptive cases by way of illustration. Clinical and laboratory indications of hypopituitarism and/or diabetes insipidus evidently should be looked for in cases of known sarcoidosis; and, vice versa, evidence of sarcoidosis should be sought in cases of unexplained hypopituitarism and/or diabetes insipidus. In this latter group, recognition of the etiology is particularly important because of the generally gratifying response to steroid therapy.

Arteritis in Rheumatoid Arthritis

Frank R. Schmid, Norman S. Cooper, Morris Ziff and Currier McEwen

The development of arteritis in patients with rheumatoid arthritis is being noted with increasing frequency and interest, and its significance has caused much speculation. The phenomenon is here subjected to careful scrutiny, on the basis of personally observed cases and reports in the literature. Arteritis, necrotizing and non-necrotizing, occurs in the more advanced and protracted cases of rheumatoid arthritis, is probably responsible for such systemic manifestations as pericarditis, episcleritis and peripheral neuritis, and is apt to make itself known clinically rather abruptly. The arterial lesions tend to heal, the clinical manifestations slowly to subside. The authors do not believe that arteritis is the primary lesion of rheumatoid arthritis, as has been suggested, but rather only an occasional complication of the underlying disorder. What causes this complication is not clear; the evidence here cited does not suggest that corticosteroid therapy is solely or chiefly responsible.

The Mild Hemophilias. Occult Deficiencies of AHF, PTC and PTA Frequently Responsible for Unexpected Surgical Bleeding

Paul M. Aggeler, M. Silvija Hoag, Ralph O. Wallerstein and Dorothy Whissell

Attention is called to the prevalence of AHF, PTC and PTA deficiencies of a degree insufficient to prolong the clotting time and often associated with an inconspicuous history of "spontaneous" prolonged bleeding, but enough to cause severe and even fatal hemorrhage after surgery or external trauma. These conditions are best recognized by testing for impaired thromboplastin generation and by close questioning for a family history of bleeding, so as to forestall prolonged hemorrhage after surgery; the usual perfunctory preoperative clotting time measurement is inadequate for the purpose. A general discussion of the whole problem adds to the interest and instructiveness of the paper.

Studies on the Relationship of Temperature to Sickle Cell Anemia

EDWARD RUBENSTEIN 95
res prevailing in the lower part of the

This study makes the interesting point that the low temperatures prevailing in the lower part of the leg lead to increased viscosity of the blood in sicklemia and thus may account for the prevalence of leg ulcers in this disease.

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AN AMES CLINIQUICK

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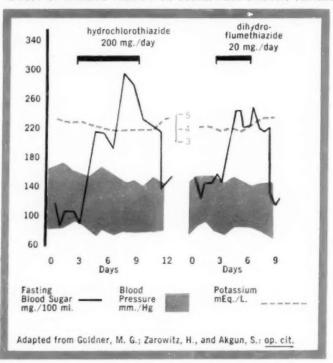
can treatment of hypertension with thiazide diuretics either precipitate or aggravate diabetes?

In susceptible patients, thiazide derivatives may unmask a prediabetic state or aggravate existing diabetes. Fatigue and polyuria—with or without glycosuria—may be due to diabetes as well as to potassium loss and diuresis. This phenomenon is readily reversible and does not contraindicate the use of thiazides in hypertensive diabetics, but does warrant close supervision of all such patients to avoid impairment of their diabetic control.

Source:

Goldner, M. G.; Zarowitz, H., and Akgun, S.: New England J. Med. 262:403, 1960.

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Ackerman, R. F.; Williams, E. F., Jr.; Packer, H.; Hawkes, J. H., and Ahler, J.: Diabetes 7:398, 1958.

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NUMBER ONE

Jaundice in Hodgkin's Disease

RUVEN LEVITAN, HENRY D. DIAMOND AND LLOYD F. CRAVER

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An analysis of the multiple pathogenesis of jaundice in patients with Hodgkin's disease, based on a large personal experience and review of the literature. At necropsy, in their own series of fifty-seven such patients, jaundice was attributable in 70 per cent of the cases to invasion of the liver by Hodgkin's granuloma, and in only 3.5 per cent to extrahepatic biliary tract obstruction by enlarged nodes. In a substantial proportion of cases (14 per cent) the cause of jaundice was not made clear even at autopsy. In 5.2 per cent of cases hemolytic jaundice related to Hodgkin's disease was present. These questions of mechanisms are not altogether academic, as is brought out, since the plan of treatment may depend upon the posited cause. Many other points of interest are brought out.

Reviews

Parathyroid Hormone. Nature and Mechanism of Action . . . Howard Rasmussen

112

Having already succeeded brilliantly in isolating a highly purified, homogeneous parathyroid hormone preparation, and having shown that this single polypeptide affects both calcium and phosphorus metabolism, Dr. Rasmussen attempts here to construct a unifying theory to account for the multiple actions of the parathyroid hormone on the handling of calcium and phosphorus by the bones, kidney, intestine and mammary gland. With the incomplete and conflicting data available in the literature, this takes a bit of doing, but is accomplished by ingenious if not always convincing selection, spiced with speculation. The primary objective is to maintain constancy of the calcium ion activity in the plasma. The parathyroid hormone assists by (1) increasing the rate of calcium (and phosphorus) resorption from bone, (2) increasing renal tubular reabsorption of calcium and secretion of phosphate, and (3) increasing the rate of absorption of calcium from the gut. When the plasma calcium ion concentration is excessive, a feedback mechanism restores equilibrium by shutting off parathyroid secretion, and increasing deposition in bone and urinary and fecal excretion. Such apparent discrepancies as early hyperphosphaturia after injection of the hormone in man can be explained by these mechanisms in an ingenious manner that may have wider implications.

Cushing's Syndrome. A Study of Fifty Patients

Louis J. Soffer, Angelo Iannaccone and J. Lester Gabrilove

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A detailed analysis of the clinical, laboratory and pathologic findings in fifty cases of Cushing's syndrome due to adrenal carcinoma in thirteen instances, benign adrenal tumor in eight, and associated with non-tumorous adrenals in twenty-nine. Of special interest is the assessment of current methods of diagnosis in each category of morphologic adrenal abnormality, and the authors' experience with modern treatment of the disorder, again separated (for reasons of therapy of choice, and outcome) into non-tumorous and tumorous cases.

Segmental Consolidation of the Lung J. Richard Johnson and Lester E. Bauer

The segmental anatomy of the lung, well known to the chest physician, radiologist and thoracic surgeon, should be more familiar to others, as this lucid review makes clear. The text is informatively illustrated to show the radiographic localization of the various bronchopulmonary segments. Of great value in diagnosis is the anatomic predilection of specific lung lesions, which the authors delineate in some detail.

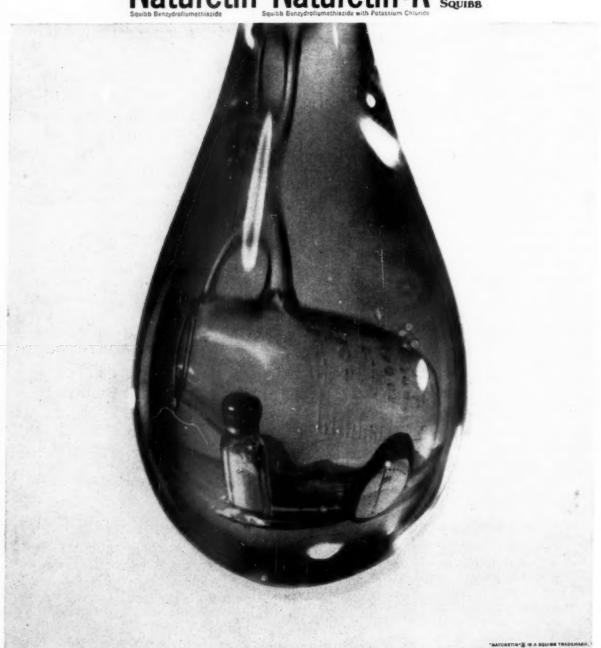
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A well studied case in which populadome was found to be associated (as accessionally accure) with	

A well studied case in which papilledema was found to be associated (as occasionally occurs) with protracted respiratory acidosis, present in spite of minimal respiratory complaints. Appropriate investigation suggested accumulation of carbon dioxide in brain tissue as the cause of the puzzling eyeground changes.

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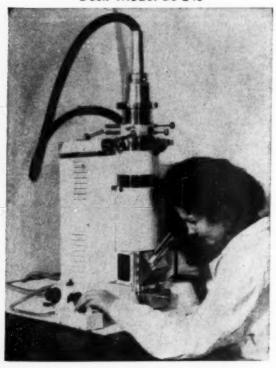
References: 1. Ford, R. V., Cur. Therap. Res., 2:51, 1960. 2. Pitts, R. F., Am. J. Med., 24:745, 1958.

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*Warter, P. J.: Prednisolone-hydroxyzine combination in rheumatoid arthritis, J. M. Soc. New Jersey 54:7, 1957.



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Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1969, p. 661.



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Supply: Tablets 5 mg., bottles of 100. Emulsion, 1-cc. ampuls containing 10 mg. and 50 mg. per cc.; boxes of 6 ampuls.

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ADDITIONAL DATA

On the comparison of Potassium Penicillin V and Synthetic Penicillin

1 On antibacterial activity in the serum

In a recent, follow-up study¹ involving a number of penicillins, McCarthy and Finland compared the antibacterial activity of potassium penicillin V and synthetic penicillin. They wrote: "Penicillin V provided greater activity than phenethicillin [synthetic penicillin] against the streptococcus and pneumococcus, at least equivalent activity against staphylococcus and sarcina in the serum and the same or greater activity in the urine although the concentrations of phenethicillin were higher and a slightly greater proportion of the latter was recovered from the urine."

In other comment on the two penicillins, they stated: "Thus, although the claim of better absorption and excretion and higher serum level of phenethicillin may be partly correct, strictly speaking, this is true in a very restricted sense and is therapeutically meaningless. Indeed the claim is misleading since it clearly implies greater antibacterial and presumably curative activity, which, in fact, the drug does not possess..."

In an earlier study², the same investigators found that the two penicillins "are absorbed in essentially the same manner in normal men and produce comparable levels of antibacterial activity in the serum."

A direct laboratory comparison³ by Abbott scientists revealed a measurable difference in activity, milligram for milligram, between the two penicillins in vitro. Against four pathogenic strains (staphylococcus, streptococcus, pneumococcus, and corynebacterium species), potassium penicillin V exhibited from two to eight times the antibacterial activity of synthetic penicillin. In another study, Griffith⁴ found that penicillin V not only produced peak levels of serum antibacterial ac-

tivity faster, but produced values almost half again as high as those obtained with synthetic penicillin.

2 On resistance to penicillinase

In another recent report, Geronimus⁵ commented on this aspect of the new penicillin. He concluded after analyzing the current data: "Very large concentrations of alphaphenoxyethyl penicillin (phenethicillin or penicillin-152) were required to inhibit even so-called moderately penicillin-resistant staphylococci when populations were employed that approached those found in vivo. Inferences regarding the possible effectiveness of phenethicillin in infections by penicillinase-producing staphylococci drawn by others from experiments with relatively minute inocula were found to be unwarranted."

McCarthy et al.² reached a similar conclusion stating: "Both of these penicillins [potassium penicillin V and phenethicillin] are qualitatively similar to penicillin G in their susceptibility to penicillinase produced by Staphylococcus aureus."

At Abbott, investigators studying the same subject³, found that the rate of destruction of all three penicillins was so great that any differences were of no therapeutic significance.

3 On the comparative safety of oral penicillin

In 1957, a nationwide survey⁶ of antibiotic reactions was made. One of the conclusions reached by the investigators in regard to penicillin reactions was: "It is clear also that the oral route is the much safer method of administration, both from the standpoint of numbers

COMPOCILLIN®VK

Potassium Penicillin V)

offers greater antibacterial activity against penicillin-sensitive organisms

of reactions and of mortality." Neither this survey, nor any evidence presented since, indicates that any form of oral penicillin is less allergenic than another oral form.

On the recent claims of synthetic penicillin

Recently, the New England Journal of Medicine editorially reviewed the status of the two penicillins. The article concluded: "It thus appears that the major claims of phenethicillin over penicillin V are not well founded. More data are needed to permit a complete comparison of these and other penicillins, particularly in their effects on infections caused by penicillinase-producing staphylococci, but it is fair to say that the new, so-called synthetic penicillin possesses no demonstrated virtue of importance that should impel one to choose over other available forms."

And in England, where synthetic penicillin was first discovered and marketed, the British Medical Journal (after studying a commercial brochure) editorialized:"There is no evidence of any activity superior to that of other penicillins against Gram-negative species, and what differences there are against sensitive species are in favour of penicillin G or V or both; this applies to all varieties of streptococci tested."8

On the advantages of Compocillin-VK

Compocillin-VK (potassium penicillin V) offers early, high concentrations of serum antibacterial activity against penicillin-sensitive organisms. Following appropriate doses, initial activity levels are higher than those obtained with intramuscular penicillin G. And normally, patients respond just as well as with the injectable.

Additionally, Compocillin-VK (potassium penicillin V) offers an easy-to-take form for every patient—any age. It comes as tiny, Filmtab® tablets, 125 mg. (200,000 units) and 250 mg. (400,000 units). And as granules for Oral Solution. When reconstituted, each tasty 5-ml. teaspoonful provides a fresh, cherry-flavored solution containing 125 mg. of potassium penicillin V.

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- 8. Editorial: A New Penicillin, Brit. M. J., 2:940, Nov. 7, 1959.

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Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, as indicated by prothrombin time determinations.

Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958.
 Moser, K. M.: Disease-a-Month, Chicago, Yr. 8k. Pub., Mar., 1960, p. 13.
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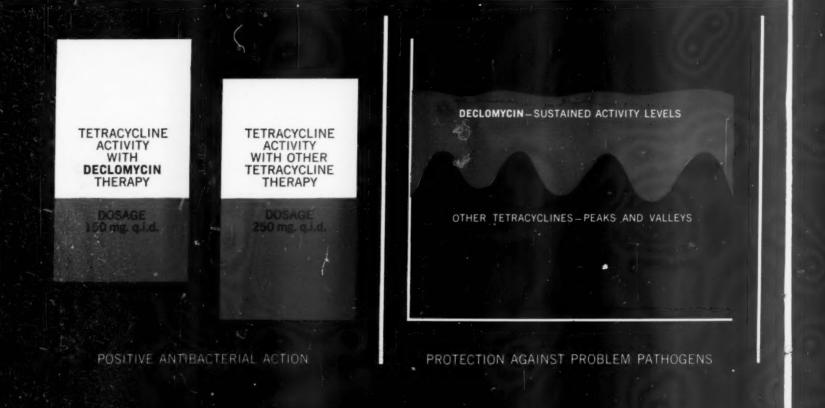
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attains activity levels promptly

DECLOMYCIN Demethylchlortetracycline attains — usually within two hours—blood levels more than adequate to suppress susceptible pathogens—on daily dosages substantially lower than those required to elicit antibiotic activity of comparable intensity with other tetracyclines. The average, effective, adult daily dose of other tetracyclines is 1 Gm. With DECLOMYCIN, it is only 600 mg.

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retains activity levels 24-48 hrs.

DECLOMYCIN Demethylchlortetracycline retains activity levels up to 48 hours after the last dose is given. At least a full, extra day of positive action may thus be confidently expected. The average, daily adult dosage for the average infection—1 capsule q.i.d.—is the same as with other tetracyclines…but **total** dosage is lower and duration of action is longer.

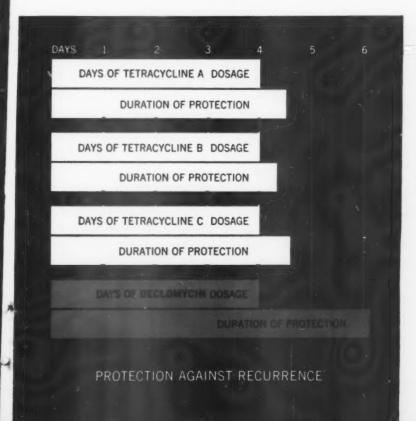
CAPSULES, 150 mg., bottles of 16 and 100. **Dosage:** Average infections—1 capsule four times daily. Severe infections—Initial dose of 2 capsules, then 1 capsule every six hours.

PEDIATRIC DROPS, 60 mg./cc. in 10 cc. bottle with calibrated, plastic dropper. **Dosage:** 1 to 2 drops (3 to 6 mg.) per pound body weight per day—divided into 4 doses.

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PRECAUTIONS—As with other antibiotics, DECLOMYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid exposure to intense sunlight. If adverse reaction or idiosyncrasy occurs, discontinue medication.

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tentabs contain an unexcelled antihistamine, Dimetane, which has produced good to excellent results in thousands of cases of allergic respiratory disorders.* In DIMETAPP Extentabs, the action of Dimetane with two outstanding decongestants—phenylephrine and phenylpropanolamine—promptly dries secretions and reduces edema and congestion in the nose, the sinuses, and the upper respiratory tract.

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Dosage: Adults –1 Extentab q. 8-12 hours. Children over 6 –1 Extentab q. 12 hours. Administer with caution to patients with cardiac or peripheral vascular diseases and hypertension, and to those sensitive to antihistamines. See package insert for further details. **Supplied:** bottles of 100 and 500. "Full bibliography on Dimetane available on request.

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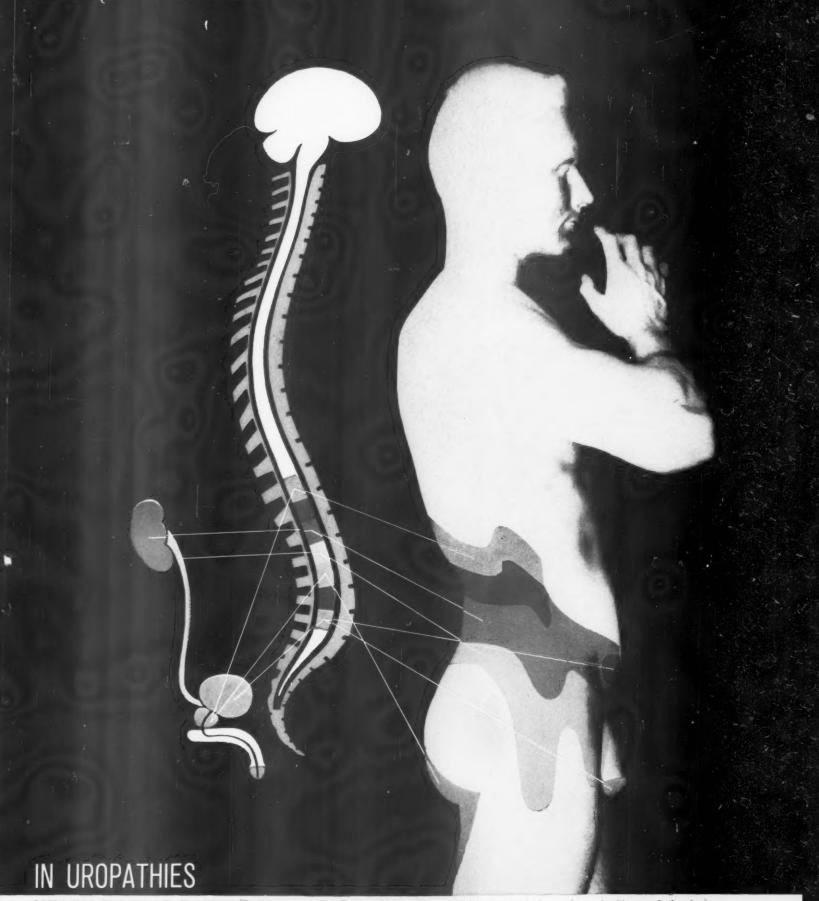
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In previous studies,^{2,3} the author employing a 48 hour intubation technique—reported a marked reduction in both volume and acidity of nocturnal gastric secretion in ulcer patients, following administration of Tral 75 mg. Gradumet.

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In its new 75 mg. form, Tral Gradumet actually "meters" its release so that the patient is receiving a measured dose of Tral at each point during the sleeping interval. Maximum release is timed to coincide with the critical 2:00 to 4:00 a.m. peak period of nocturnal secretion and discomfort. The unique Gradumet release principle is not dependent on pH, motility, enzymatic activity or other variables. In fact, the release rate is so predictable that it can be expressed as an algebraic equation.

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1. Kasich, A. M., Relief of Nocturnal Pain in Dudenal Ulcer, Am. J. Gastroenterol., 33:66, January, 1960. 2. Kasich, A. M. and Fein, R. D., Hexocyclium Methosulfate in Active Duodenal Ulcer: Evaluation of a New Anticholinergic Drug in Conventional and Long-Acting Forms, Especially its Effect on Gastric pH as studied in 48-hour Analysis, Am. J. Digest. Dis., 3:12, January, 1958. 3. Kasich, A. M., Hexocyclium Methosulfate, a New Anticholinergic Drug in Conventional and Long-Acting Forms: Its Effect on Gastric Secretion, Schweiz. Ztschr. allg. Path., 21:354, 1958. %Tral Gradumet — Hexocyclium Methylsulfate in Long-Release Dose Form², Abbott. 'Patent applied for. & Filmtab—Film-sealed tablets, Abbott.

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- 1. Schluger, J. et al.: Am. J. Med. Sci. 233:296, 1957.
- 2. Bradwell, E. K.: Acta med. scand. 146:123, 1953.
- 3. Truitt, E. B. et al.: J. Pharm. Exp. PDR Ther. 100:309, 1950.



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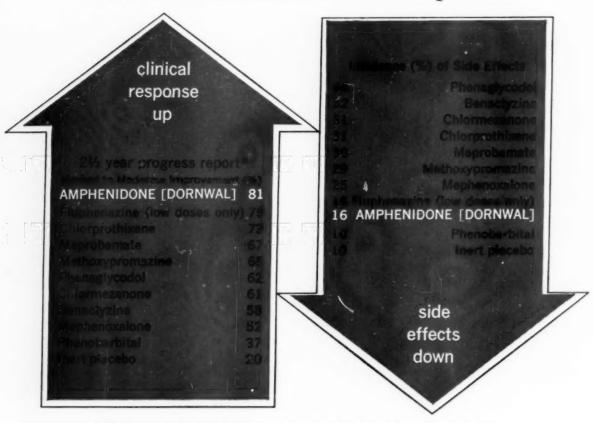
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*Nodine, J. H.; Bodi, T.; Slap, J.; Levy, H. A., and Siegler, P. E.: Human bioassay of tranquilizers in psychosomatic disorders, Scientific Exhibit, American Medical Association Annual Meeting, Miami Beach, Florida, June 13-17, 1960.

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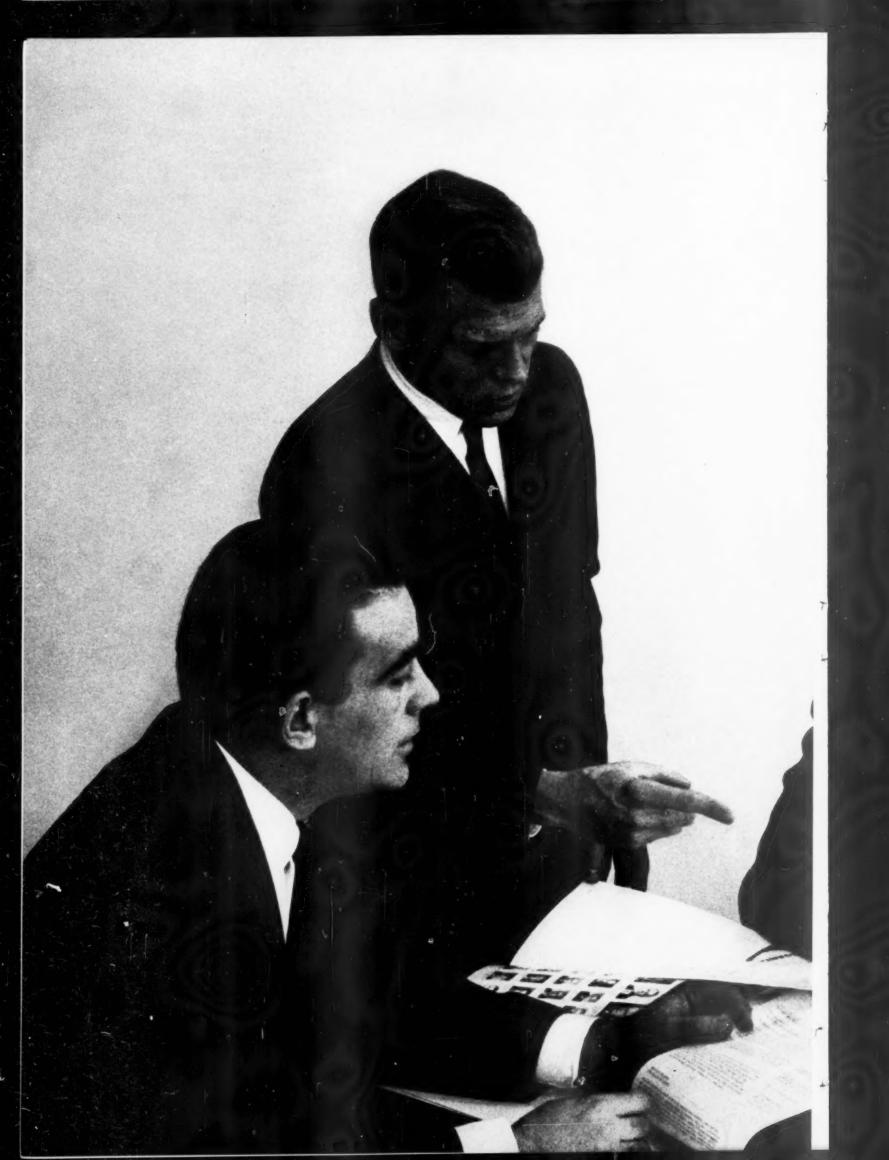
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May be chewed, dissolved in mouth, or swallowed with water. Each white, mint-flavored tablet contains glycine 0.18 Gm. and Ca carbonate 0.42 Gm. Bottles of 100.

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LITERATURE SUPPLYING DETAILS OF DOSAGE AND ADMINISTRATION AVAILABLE ON REQUEST. (1) Abraham, W., in Green, J. R., & Steelman, H. F.: Epileptic Seizures, Baltimore, Williams & Wilkins Company, 1956, p. 132. (2) Crawley, J. W.: M. Clin. North America 42:317 (March) 1958. (3) Bray, P. F.: Pediatrics 23:151, 1959.



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Rit	ooflavin									*	,							10 mg.
Co	balamin																	20 mcg.
Nic	cotinami	de			۰			0						0				50 mg.
Py	ridoxine	hy	dr	oc	hle	ori	d€				0				0	0		1 mg.

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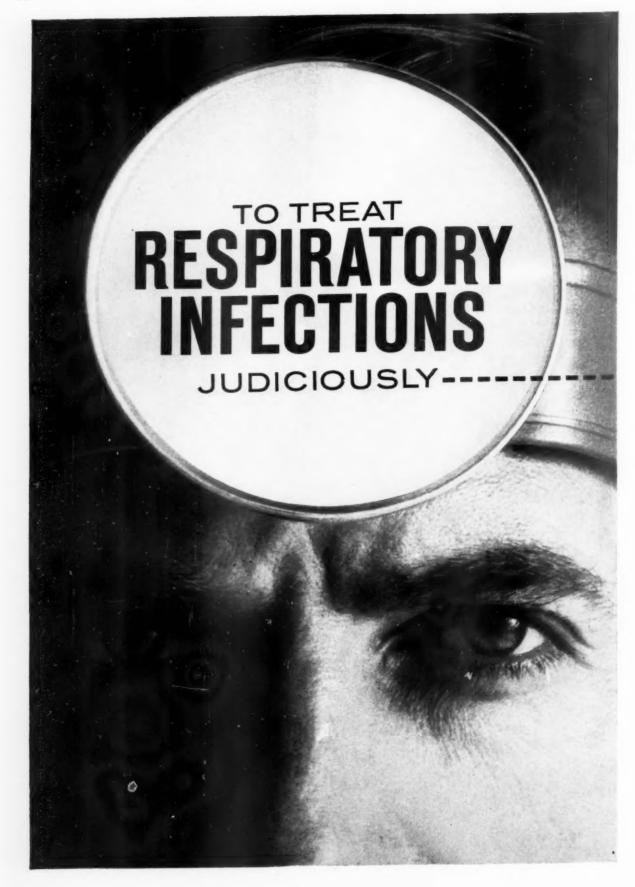
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When it's penicillin-susceptible and the patient is not allergic Use an orally maximal penicillin



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Literature on request

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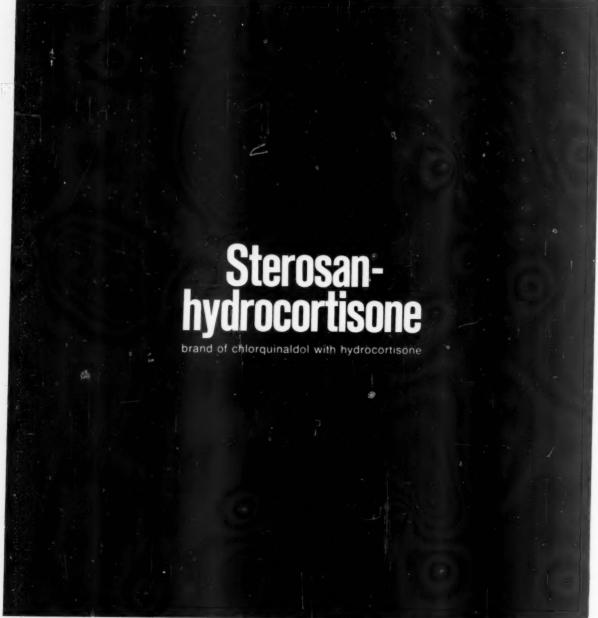
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Literature on request

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New York 17, N. Y., Division, Chas. Pfizer & Co., Inc. Science for the World's Well-Being $^{\rm TM}$



hastens healing of most dermatoses

In most of the common dermatoses, infection, inflammation and allergy...either singly or in combination...play a critical etiologic role. By virtue of its dual components Sterosan-hydrocortisone effectively combats all three factors. As a result, Sterosan-hydrocortisone in clinical use effectively brings about healing in 80-90% of dermatoses¹⁻⁴...is often effective in cases of long duration resistant to other topical therapy.²⁻⁴ Available in both cream and ointment form, Sterosan-hydrocortisone is light in color...cosmetically acceptable for use on exposed areas.

References: (1) Lubowe, I. I.: Antibiot. Med. & Clin. Therap. 4:81, 1957. (2) Fox, H. H.: Antibiot. Med. 6:85, 1959. (3) Murphy, J. C.: Rocky Mountain M. J. 55:53, 1958. (4) Pace, B. F.: Med. Rec. & Ann. 51:370, 1957.

Sterosan*-hydrocortisone, brand of chlorquinaldol with hydrocortisone, Cream and Ointment containing 3% of Sterosan and 1% of hydrocortisone. Tubes of 5 and 20 Gm.

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York

6:85, 1959. hing 3% of STH588-61 NO SPRAIN, NO STRAIN, NO LOW BACK PAIN

RELAXES, EASES ACUTE MUSCLE SPASM & PAIN

RELA achieves the necessary interruption of the spasm/pain cycle through its unique twofold myogesic^x action.

RELA restores mobility by relieving stiffness, pain and spasm.

Bibliography: 1. Ostrowski, J. P.: Orthopedics 2:7 (Jan.) 1960. 2. Kestler, O. C.: J.A.M.A. 171:2039 (April 30) 1960. 3. Frankel, K.: Paper presented at Scientific Meeting, New York State Society of Industrial Medicine, Inc., New York, Sept. 30, 1959.

Schering

* MYOGESIG: MUSCLE RELAXANT

in edema or hypertension

more doctors are prescribing—

more patients are receiving the benefits of—
more clinical evidence exists for—







than for any other diuretic-antihypertensive

DIURIL is unique. There is no other brand of chlorothiazide.

Dosage: Edema—One or two 500-mg. tablets DIURIL once or twice a day. Hypertension—One 250-mg. tablet DIURIL or one 500-mg. tablet DIURIL two to three times a day.

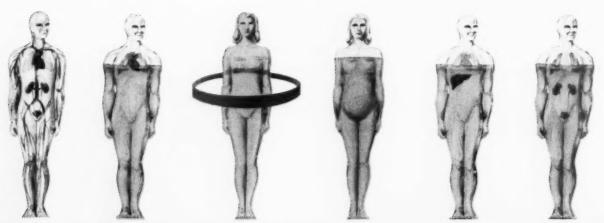
Supplied: 250-mg. and 500-mg. scored tablets DIURIL chlorothiazide in bottles of 100 and 1000.

DIURIL is a trademark of Merck & Co., INC.

Additional information is available to the physician on request.



MERCK SHARP & DOHME Division of Merck & Co., INC., West Point, Pa.

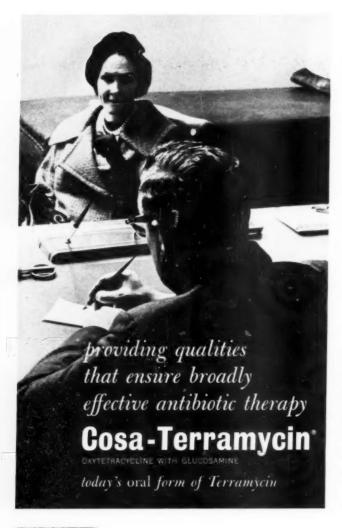


HYPERTENSION CONGESTIVE FAILURE PREMENSTRUAL TENSION EDEMA OF PREGNANCY CIRRHOSIS WITH ASCITES RENAL EDEMA

I know it is effective

a reservoir of dependable performance

Terramycin therapy



The continuing clinical effectiveness of Terramycin therapy derives as always from its proven antibiotic characteristics—rapid absorption; notably wide distribution in body tissues and fluids; high, active urinary concentrations; and a broad anti-infective spectrum embracing even such a troublesome organism as Pseudomonas. Additionally, Terramycin therapy provides the assurance of a 10-year record of exceptional toleration.

IN BRIEF

Cosa-Terramycin provides oxytetracycline (Terramycin®) with glucosamine for enhanced absorption.

INDICATIONS: Because oxytetracycline is effective against both gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain parasites (amebae, pinworms), Cosa-Terramycin is indicated in a great variety of infections due to susceptible organisms, e.g., infections of the respiratory, gastrointestinal, and genitourinary tracts, surgical and soft-tissue infections, ophthalmic and otic infections, and many others.

ADMINISTRATION AND DOSAGE: Adults: 1 Gm. of oxytetracycline daily in four divided doses is usually effective. In *severe* infections, a larger dosage (2-4 Gm. daily) may be indicated. Infants and children: 10-20 mg. of oxytetracycline per lb. of body weight daily. Certain diseases are treated in courses.

SIDE EFFECTS AND PRECAUTIONS: Antibiotics may allow overgrowth of nonsusceptible organisms — particularly monilia

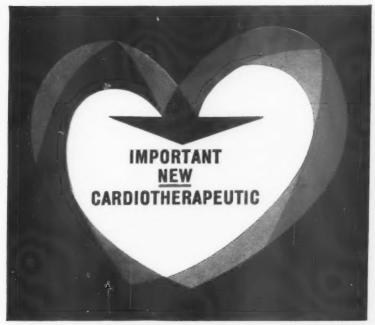
and resistant staphylococci. If this occurs, discontinue medication and institute indicated supportive therapy and treatment with other appropriate antibiotics. Aluminum hydroxide gel has been shown to decrease antibiotic absorption and is therefore contraindicated. Glossitis and allergic reactions are rare. There are no known contraindications to glucosamine.

SUPPLIED: Cosa-Terramycin Capsules, 250 mg. and 125 mg. Terramycin is also available in: Cosa-Terrabon® Oral Suspension, a palatable preconstituted aqueous suspension containing 125 mg. per 5 cc. teaspoonful, bottles of 2 oz. and 1 pint; Cosa-Terrabon® Pediatric Drops, a palatable preconstituted aqueous suspension containing 5 mg. per drop (100 mg. per cc.), bottle of 10 cc. with calibrated plastic dropper; and Terramycin Intramuscular Solution, conveniently preconstituted, in the new 10 cc. multi-dose vial, 50 mg. per cc., and in 2 cc. prescored glass ampules, containing 100 mg. or 250 mg., packages of 5 and 100. In addition, a variety of other systemic and local dosage forms are available to meet specific therapeutic requirements.

More detailed professional information available on request.



a reservoir of dependable performance— Terramycin* therapy



CARDIOQUIN®

A NEW MOLECULE QUINIDINE POLYGALACTURONATE

A NEW DIMENSION IN QUINIDINE THERAPY WHICH ASSURES ...

Avoidance of Local Gastrointestinal Irritation. 'CARDIOQUIN' TABLETS ionize slowly, avoiding "ionic flooding" and concomitant irritation of the gastrointestinal mucosa. The polar character of conventional quinidine salts allow them to strongly dissociate in physiological fluids; the resultant flood of basic and acidic ions, rapidly released, are irritating to the gastrointestinal mucosa, causing "ionic shock."

Uniformly Absorbed and Maintained Blood Quinidine Levels. 'CARDIOQUIN' TABLETS are not sustained-release tablets. The unique chemodynamics of the quinidine polygalacturonate molecule provide reliable and uniform rate of absorption of the quinidine moiety with predictable, full cardiac effects throughout induction and maintenance therapy.

Peak Blood Quinidine Levels Within 4 to 6 Hours. Measurable blood levels appear within 1 hour after administration of 'CARDIOQUIN' TABLETS and peak levels within 4 to 6 hours.

Full Quinidine Cardiodynamics. EKG changes produced by equivalent doses of quinidine polygalacturonate and quinidine sulfate show no qualitative difference.

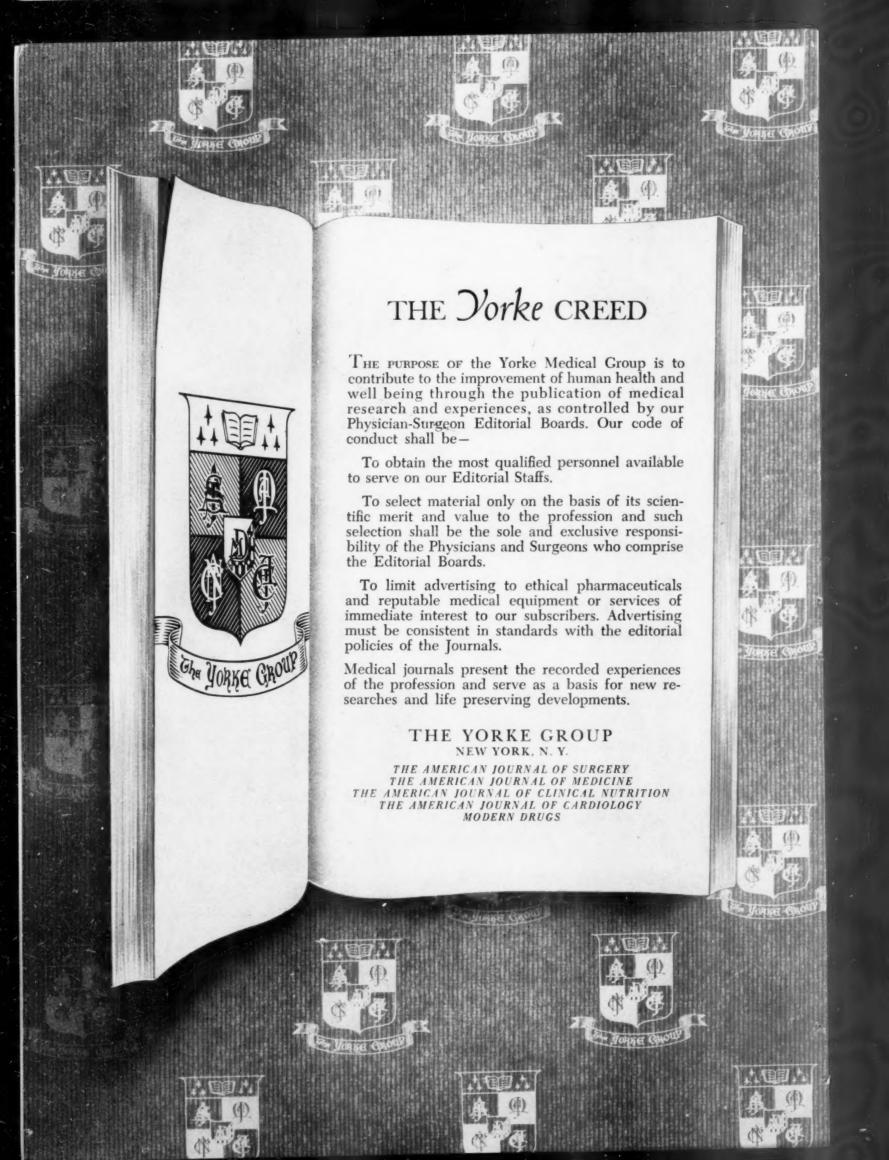
DOSAGE: Each 'CARDIOQUIN' TABLET contains the quinidine equivalent of the conventional 3 grain tablet of quinidine sulfate, thus providing facility in the calculation of starting dosage. 'CARDIOQUIN' TABLETS may be substituted one tablet for each three grain quinidine sulfate tablet (or equivalent) in patients already on other quinidine preparations. Consult Product Data Brochure, available on request, for complete directions, contraindications and precautions attending the use of the drug.

NOTE: Observe the same contraindications that apply to other quinidine preparations.

SUPPLIED: Uncoated, scored tablets in bottles of 50. Each tablet contains 275 mg. quinidine polygalacturonate [equivalent in quinidine content to 3 grains (200 mg.) of quinidine sulfate].

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You canand shouldadjust dosage with Orinase just as you do with insulin

Prescribe enough Orinase to release enough native insulin

A slight upward adjustment of Orinase dosage is often the only step needed to establish or regain optimum control of diabetes. The increase serves to make available the amount of Orinase-released native insulin required by the patient. The change may be made freely, to 3 grams or more a day, because Orinase has virtually no "ceiling" imposed on dosage by toxicity or untoward effects.

To maintain smooth control, to avoid needless "secondary failures," give sufficient Orinase to meet the varying needs of different patients or the varying needs of an individual patient.

1. CASE DATA COURTESY HENRY DOLGER, M.D.

EACH TABLET CONTAINS:

TOLBUTAMIDE 0.5 GM.

*Trademark, Reg. U.S. Pat. Off.-tolbutamide, Upjohn

Orinase (grams | day)

	Otthuse (gre	into (day)
6/12/57	2.0	44
8/7/57	1.0	65
10/2/57	1.0	55
11/29/57	1.0	65
1/17/58	3.0	500
2/14/58	3.0	600
3/28/58	2.0	30
5/5/58	1.5	000

Actual doses used to maintain optimum control in patient J.S., male, age 54¹

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

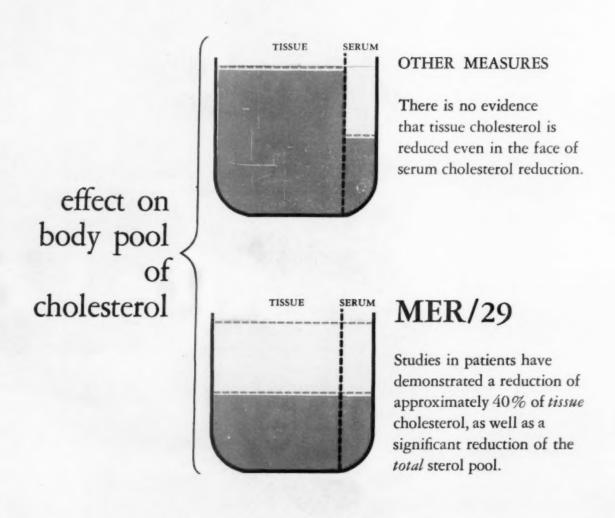
Upjohn

For those diabetics who won't stick to their diets, add appetite-suppressing Didrex! (benzphetamine, 50 mg. per tablet).

†Trademar



how MER/29 differs from other cholesterol-lowering measures...



- ... the first cholesterol-lowering agent to inhibit the formation of cholesterol within the body, reducing both tissue and serum cholesterol
- ... the only specific cholesterol-lowering agent: no demonstrable interference with other vital biochemical processes reported to date; toleration and absence of toxicity established by more than 2 years of clinical investigation
- ... convenient dosage: one 250 mg. capsule daily before breakfast

... and how these differences can benefit your patients particularly the coronary artery atherosclerosis

particularly those with high cholesterol levels, coronary artery disease, and generalized atherosclerosis

MER/29 REDUCES CHOLESTEROL IN 8 OUT OF 10 PATIENTS: MER/29 reduces both serum and tissue cholesterol, *irrespective of diet*. Although some physicians prefer to use MER/29 in conjunction with controlled diets, cholesterol can be reduced successfully without such limitation.

CONCURRENT BENEFITS REPORTED IN SOME PATIENTS: In angina patients, some of the concurrent benefits reported include decreased incidence and severity of attacks, improved ECG patterns, diminished nitroglycerin dependence, and increased sense of well-being.

DIRECT, SPECIFIC CHOLESTEROL-LOWERING ACTION WITH MER/29: Some agents used to reduce cholesterol have other important primary effects—such as hormonal or vasodilator action. The primary, the *only* known function of MER/29 is to reduce cholesterol.

MER/29 HAS PRODUCED FEW SIDE EFFECTS, NO TOXICITY: Patients have been treated with MER/29 for continuous periods up to 19 months. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy. MER/29 is compatible with other cardiovascular therapies. It can be used along with measures which control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. These include nitroglycerin and PETN, and there have been no reports to date of incompatibility with anticoagulants.

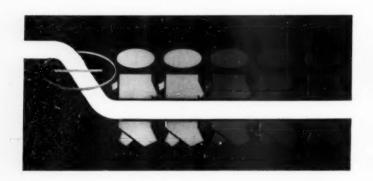
CAUTION: Since long-term MER/29 therapy may be necessary, periodic examinations, including liver-function tests, are desirable. Also, since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug is contraindicated in pregnancy.

SUPPLIED: Bottles of 30 pearl gray capsules.

Complete bibliography and product information available on request.



WHICH DIABETES THERAPY FOR THE "DIET FAILURE"?



Diabinese®

the oral antidiabetic most likely to succeed

for example—when diet alone has failed because of poor cooperation, impracticability, or inadequate control of hyper-glycemia, consider diet plus DIABINESE. Extensive experience has shown that DIABINESE can assure better control "in that large segment of the diabetic population that does not fully cooperate in the dietary management." Mild cases have been effectively controlled with a single daily dose of 100 mg. or less.²

FOR MAXIMAL ASSURANCE OF CONTINUOUS BLOOD-SUGAR CONTROL WITH ORAL THERAPY—DIABINESE

^{1.} Handelsman, M. B.; Levitt, L., and Calabretta, M. F.: Ann. New York Acad. Sc. 74:632, 1959.

^{2.} A.M.A. Council on Drugs: J.A.M.A. 172:57, 1960.

to ensure control where diet alone has failed

to replace or reduce insulin dosage

to realize the full potential of oral therapy

IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, diabinese often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe non-ketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, diabinese dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently

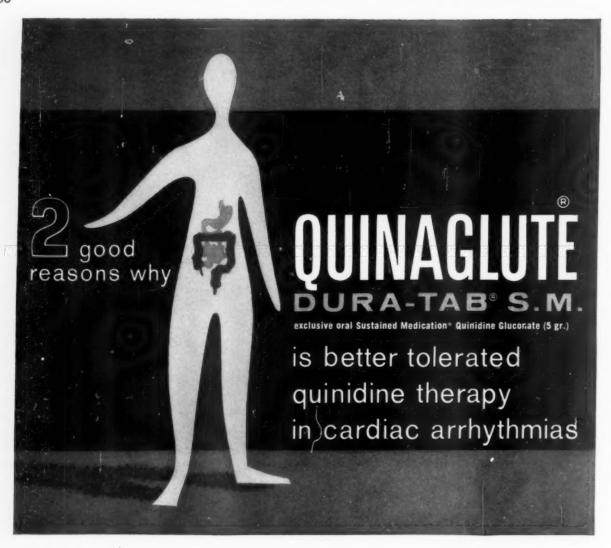
on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, diabinese should be discontinued.

PRECAUTIONS AND CONTRAINDICA-TIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

More detailed professional information available on request.





quinidine gluconate (in Quinaglute Dura-Tab S.M.) is ten times as soluble as quinidine sulfate — and easier on the g.i. tract.

whereas the total daily dose of quinidine sulfate is released largely in the stomach, only a fraction of Quinaglute quinidine contacts gastric membranes—the balance being slowly released and absorbed along the intestinal tract.

q. 12 h. dosage maintains uniformly effective blood levels — Quinaglute Dura-Tab S.M., a quinidine of choice in atrial fibrillation, flutter, premature contractions, auricular tachycardia. Bottles of 30, 100 and 250.

also available:
INJECTABLE QUINAGLUTE
10 cc. Multiple Dose Vials,
0.08 Gm. Quinidine
Gluconate per cc.

Samples and literature - write . . .

WYNN

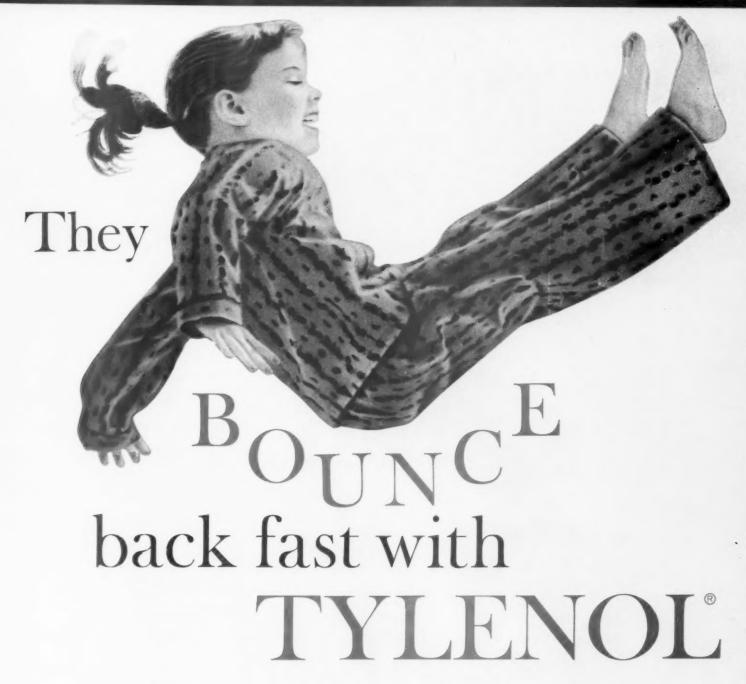
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Lancaster Ave. at 51st St., Philadelphia 31, Pa.

For dosage, etc.



PAGE 821



she's flying high now...her temperature and discomfort brought under control quickly with Tylenol*

TYLENOL®

an effective pediatric antipyretic and analgesic¹ remarkably free from toxicity² well accepted, well tolerated by children¹

TYLENOL ELIXIR—120 mg. (2 gr.) per 5 cc.; 4 and 12 fl. oz. bottles.

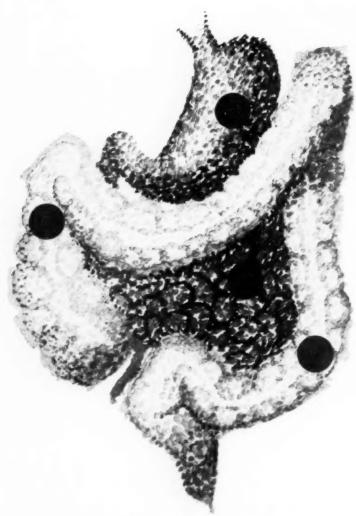
TYLENOL DROPS—60 mg. (1 gr.) per 0.6 cc.; 15 cc. bottles with calibrated droppers.



MCNEIL LABORATORIES, INC., PHILADELPHIA 32, PA.

Cornely, D. A., and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Antipyretic-Analgesic, J.A.M.A. 160-1219 (Apr. 7) 1956

^{2.} Mintz, A. A.: Management of the Febrile Child, J. Ky. Acad. Gen. Pract. 5:26 (Jan.) 1959.



for peptic ulcer...

for gastrointestinal disorders, specify

SUSTAGEN

COMPLETE THERAPEUTIC NUTRIMENT

to help restore and maintain good nutrition

in peptic ulcer

Sustagen "...systematically enhances healing of the ulcer and restoration of the patient to a state of optimal nutrition."

in ulcerative colitis

"...high protein, high carbohydrate, high caloric, low residue diet" imperative. Sustagen provides this diet.

provides all essential nutrients

Sustagen may be used as the sole source of food or to fortify the diet—helps build and repair tissue, restore nitrogen balance, enhance rehabilitation.

orally-or by tube

Palatable,³ easy to take in beverage form —just one glass provides 390 calories and 23.5 Gm. protein. In tube feeding Sustagen alone provides complete nutrition. Mixes and flows readily. Bland, low in bulk, low in fiber, it is well tolerated—easy to use, easy to take.

References:

(1) Winkelstein, A.: Am. J. Gastroenterol. 27:45-52 (Jan.) 1957. (2) Brown, C. H.: Am. Pract. & Digest Treat. 9:405-411 (March) 1958. (3) Winkelstein, A., and Schweiger, E.: J.A.M.A. 160:1111-1113 (March 31) 1956.



trouble-free
for the
hypertensive patient

RAUWILOID

alseroxylon, 2 mg.

worry-free for the physician



Just 2 tablets at bedtime

Eight years of continuous use...some 600,000,000 patient-days of effective, safe therapy with RAUWILOID ...prove enduring patient-acceptance and physician-satisfaction...without any revisions of claims, changes of dosage, or additional side actions encountered.

RAUWILOID

is an original development of



for functional disorders of menopause...
cardiac neuroses...
interval treatment of headache



BELLERGAL effectively relieves distress of hot flashes * sweating * headach

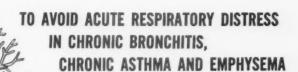
large effectively relieves distress of hot flashes * sweating * headache * excessive fatigability * irritability * palpitation * insomnia

"A double blind study shows that the integrative action of ... Bellergal Spacetabs is well suited for the symptomatic treatment of patients with vasomotor symptoms. Excellent to good results were achieved in 78 per cent of all complaints in all ambulatory patients treated with Bellergal Spacetabs... Symptoms of autonomic instability in patients with psychosomatic disorders alone, in those in the menopause, or in those in whom it was concomitant with organic disease were well controlled." Bernstein, A. and Simon, F.: Angiology 9:197, August 1958.

BELLERGAL SPACETABS — Bellafoline 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg. Dosage: 1 in the morning, and 1 in the evening.

BELLERGAL TABLETS — Bellafoline 0.1 mg., ergotamine tartrate 0.3 mg., phenobarbital 20.0 mg. Dosage: 3 to 4 daily. In more resistant cases, dosage begins with 6 tablets daily and is slowly reduced.





Choledyl remains a uniformly effective bronchodilator throughout prolonged therapy, and it is virtually free of gastric irritation and other unwanted effects even in geriatric patients.

SUPERIOR BRONCHODILATATION

THROUGH SUPERIOR THEOPHYLLINE ABSORPTION

Choledyl is often effective when aminophylline or other xanthines fail, because it produces up to 75% higher theophylline blood levels than equivalent doses of aminophylline. Depend on Choledyl to relieve bronchospasm, coughing and wheezing . . . to increase vital capacity... to ease expectoration.

THE CHOLINE SALT OF THEOPHYLLINE

betters breathing . . . decreases wheezing



Supplied: 200 mg. tablets (yellow); bottles of 100. Full dosage information, available on request, should be consulted before initiating therapy.

resistant
staphylococci
among
outpatients
emerge
less
frequently...
disappear
more
readily

CHLOROMYCETIN

chloramphenicol, Parke-Davis

"Resistance to chloramphenicol was surprisingly infrequent (0-5%)" among strains of staphylococci isolated from outpatients over a 5-year period. It was impressive to note that less than 6% of 310 strains isolated from patients treated in the emergency room were resistant to CHLOROMYCETIN. Moreover, it would appear "...that chloramphenicol-resistant staphylococci disappear more readily after leaving the hospital environment." 1

Goslings and Büchli² report that "...resistance was lost entirely after 3 months..." in the small percentage of patients who carried staphylococcal strains resistant to CHLOROMYCETIN. Numerous other investigators concur in the observation that staphylococcal resistance to CHLOROMYCETIN is of a low order.³⁻⁸

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

References: (1) Bauer, A. W.; Perry, D. M., & Kirby, W. M. M.: J.A.M.A. 173:475, 1960. (2) Goslings, W. R. O., & Büchli, K.: Arch. Int. Med. 102:691, 1958. (3) Goodier, T. E. W., & Parry, W. R.: Lancet 1:356, 1959. (4) Fisher, M. W.: Arch. Int. Med. 105:413, 1960. (5) Petersdorf, R. G., et al.: Arch. Int. Med. 105:398, 1960. (6) Glas, W. W., in Symposium on Antibacterial Therapy, Michigan & Wayne County Acad. Gen. Pract., Detroit, September 12, 1959, p. 7. (7) Modarress, Y.; Ryan, R. J., & Francis, Sr. C. E: J. M. Soc. New Jersey 57:168, 1960. (8) Rebhan, A. W., & Edwards, H. E.: Canad. M. A. J. 82:513, 1960.

IN VITRO SENSITIVITY OF COAGULASE-POSITIVE STAPHYLOCOCCI TO CHLOROMYCETIN FROM 1955 TO 1959*

1955		96%
1956		100%
1957		96%
1958		95%
1959	3	95%

These sensitivity tests were done by the disc method on 310 strains of coagulase-positive staphylococci. Strains were isolated from patients seen in the emergency room. It should be noted that among inpatients, resistant strains were considerably more prevalent.

*Adapted from Bauer, Perry, & Kirby1

10260

PARKE-DAVIS

PARKE, DAVIS & COMPANY - DETROIT 32. MICHIGAN



Photos used with patient's permission.

How new Dianabol rebuilt muscle tissue in this underweight, debilitated patient

Patient was weak and emaciated before Dianabol. R. C., age 51, weighed 160 pounds following surgery to close a perforated duodenal ulcer. His convalescence was slow and stormy, complicated by pneumonia of both lower lobes. Weak and washed out, he was considered a poor risk for further necessary surgery (cholecystectomy). Because a conventional low-fat diet and multiple-vitamin therapy failed to build up R. C. sufficiently, his physician prescribed Dianabol 5 mg. b.i.d.

Patient regains strength on Dianabol. In just two weeks R. C.'s appetite increased substantially; he had gained 9½ pounds of lean weight. His muscle tone was improved, he felt much stronger. After 4 weeks, he weighed 176 pounds. Biceps measurement increased from 10" to 11½". For the first time since onset of postoperative pneumonia, his chest was clear. Mr. C.'s physician reports: "He tolerated cholecystectomy very well and one week postop felt better than he has in the past 2 years."



Dianabol: new, low-cost anabolic agent

By promoting protein anabolism, Dianabol builds lean tissue and restores vigor in underweight, debilitated, and dispirited patients. In patients with osteoporosis Dianabol often relieves pain and increases mobility.

As an anabolic agent, Dianabol has been proved 10 times as effective as methyltestosterone. Yet it has far less androgenicity than testosterone propionate, methyltestosterone, or norethandrolone.

Because it is an oral preparation, Dianabol spares patients the inconvenience and discomfort of parenteral drugs.

And because Dianabol is low in cost, it is particularly suitable for the aged or chronically ill patient who may require long-term anabolic therapy.

Supplied: Tablets, 5 mg. (pink, scored); bottles of 100.

Complete information on request.

Dianabol® (methandrostenolone CIBA)

converts protein to working weight in wasting or debilitated patients

2/2829HB





Cremomycin_® provides rapid relief of virtually all diarrheas

NEOMYCIN—rapidly bactericidal against most intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

SULFASUXIDINE® (succinylsulfathiazole)—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

KAOLIN AND PECTIN—coat and soothe the inflamed mucosa, adsorb toxins, help reduce intestinal hypermotility, help provide rapid symptomatic relief.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

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MERCK SHARP & DOHME, DIVISION OF MERCK & CO., Inc., PHILADELPHIA 1, PA.

CREMOMYCIN AND SULFASUAIDINE ARE TRADEMARKS OF MERCK & CO., INC

anticholinergic KEEPS THE STOMACH FREE OF PAIN

tranquilizer
KEEPS
THE MIND OFF
THE STOMACH



Milpath acts quickly to suppress pain and spasm, and to allay anxiety and tension with minimal side effects.

> AVAILABLE IN TWO POTENCIES:

Milpath-400 — Yellow, scored tablets of 400 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride. Bottle of 50.

Dosage: 1 tablet t.i.d. at mealtime and 2 at bedtime.

Milpath-200 — Yellow, coated tablets of 200 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride. Bottle of 50.

Dosage: 1 or 2 tablets t.i.d. at mealtime and 2 at bedtime.

Milpath

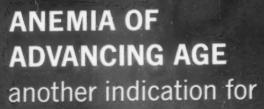
Miltown + anticholinergic

WALLACE LABORATORIES Cranbury, N. J.



Eventually he'll learn. There are no "miracle" cures for dandruff. Selsun comes close, but there are possibly 5% that it won't help at all. But for the other 95%—and that probably includes this fellow—it's the most effective treatment available. Why not give him the word—and a prescription. You'll save him money down the drain.

SELSUN® Suspension an ethical answer to a medical problem



(Intrinsic Factor Concentrate, B₁₂, Iron, With other Vitamins, Abbott)

potent antianemia therapy plus the essential B-complex

2 IBEROL FILMTABS A DAY SUPPLY:

The right amount of Iron

Ferrous Sulfate, U.S.P.....1.05 Gm. (Elemental Iron-210 mg.)

Plus the Essential B-Complex

Vitamin B₁₂ with Intrinsic Factor

Concentrate...... 1 N.F. unit (Oral)

Thiamine Mononitrate..... 6 mg.

Plus Vitamin C

Ascorbic Acid......150 mg.





THE TOTAL COLD-THERAPY TABLET nasal decongestant · analgesic antipyretic · antihistamine

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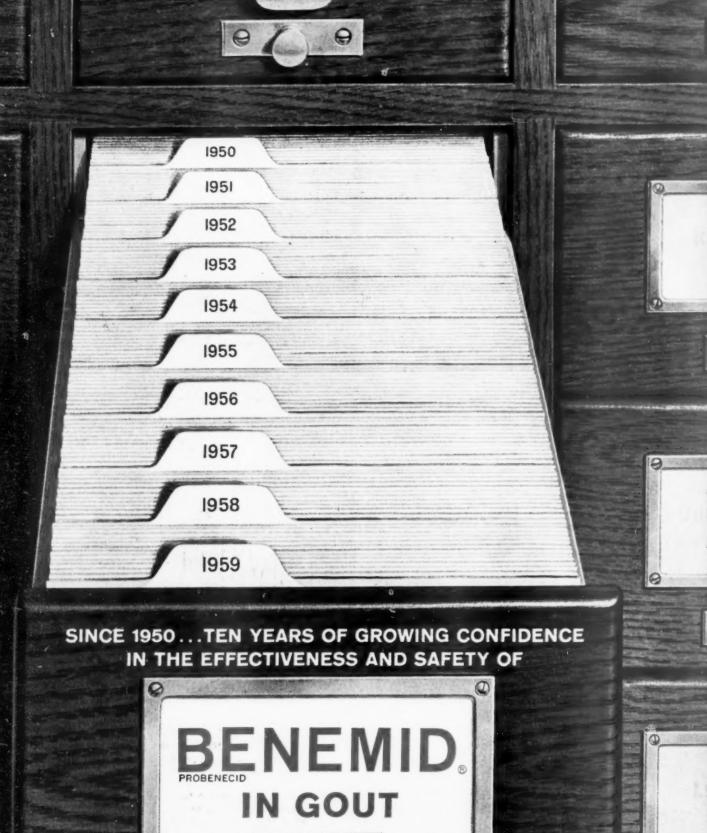
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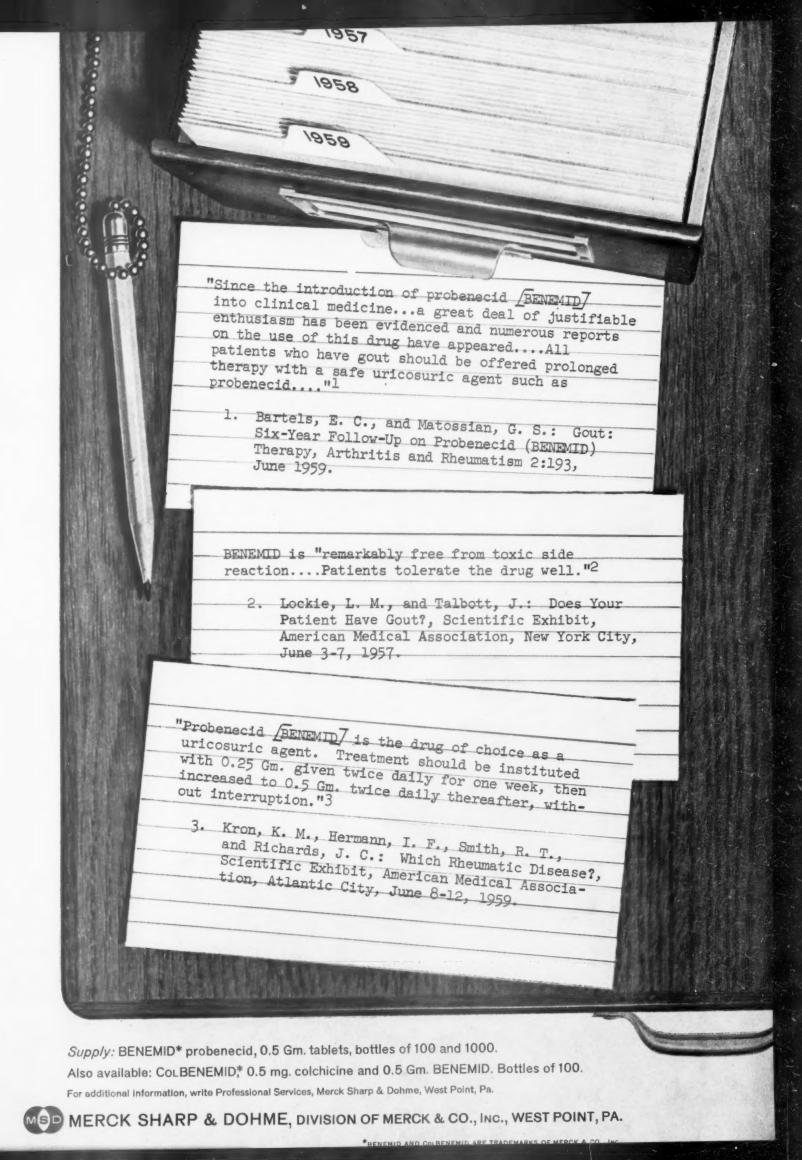
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Editorial

Genetics, Hypersensitivity and the Connective Tissue Diseases

THE relationship of the individual connective tissue diseases to each other and to a number of abnormal serum gamma globulin factors has been a subject of much recent interest. Transitional or "overlap" syndromes involving rheumatoid arthritis, systemic lupus erythematosus (S.L.E.), scleroderma, dermatomyositis and polyarteritis nodosa have been described with increasing frequency. In such patients the diagnosis of two or more of these diseases can be made simultaneously on the basis of clinical, histologic and serologic evidence.

To this group a number of other disease states have been recently linked. Both Janeway and co-workers [1] and Good and Rotstein [2] have called attention to the frequent occurrence of a polyarthritis resembling rheumatoid arthritis in patients with agammaglobulinemia. Subcutaneous nodules with histologic changes characteristic of rheumatoid nodules have appeared in a number of these subjects. Scleroderma [3] and dermatomyositis [4] also have been observed in patients with agammaglobulinemia. Recently, Bloch and his associates [5] have described the association of the ocular and parotid gland changes of Sjögten's syndrome not only with rheumatoid arthritis but also with scleroderma and S.L.E.

The connective tissue diseases tend also to share certain abnormal components of the serum gamma globulin fraction. The rheumatoid factor has been demonstrated in the serums of as many as one-third of patients with S.L.E. and with significant frequency in patients with scleroderma, dermatomyositis and polyarteritis nodosa [6]. It has been detected in almost all patients with Sjögren's syndrome, irrespective of the presence or absence of arthritis [5]. The L.E. factor is commonly found in up to 25 per cent of patients with rheumatoid arthritis. Nuclear fluorescence [5,7] and complement fixation tests [8] have demonstrated antinuclear and antiDNA reacting gamma globulin not only in patients with S.L.E. but also in patients with rheumatoid arthritis, scleroderma, dermatomyositis and Sjögren's syndrome.

The familial occurrence of rheumatoid arthritis has been demonstrated by a number of studies [9–11]. Stecher et al. [9] found it about five times as frequently in blood relatives of patients with rheumatoid arthritis as in the general population. Twin studies have shown a significantly greater incidence of rheumatoid arthritis in identical twins than in fraternal twins [12,13]. Evidence for the familial occurrence of S.L.E. has been presented most recently by Griffin and co-workers [14] and previously by a number of others. Leonhardt [15] has reported the occurrence of S.L.E. in three and hypergammaglobulinemia in eight of fourteen siblings of a single family.

The presence of the rheumatoid factor in 16 per cent of asymptomatic relatives of patients with rheumatoid arthritis has recently been shown by Ziff and co-workers [16] and confirmed by Lawrence and Ball [17]. This abnormal con-

stituent has also been demonstrated in blood relatives of patients with S.L.E. [18,19], asymptomatic and symptomatic. Biological false positive Wassermann reactions, hypergammaglobulinemia and at least one positive reaction to an L.E. cell test have also been found among asymptomatic relatives of patients with S.L.E. In addition, major rheumatic diseases, such as rheumatoid arthritis and overt S.L.E., occur

frequently in this group.

In family members of patients with agammaglobulinemia of the acquired type, not only has the rheumatoid factor been observed in asymptomatic subjects [20] but rheumatoid arthritis and possibly systemic lupus erythematosus have also been reported in significant incidence [2,8]. Positive results of tests for the rheumatoid factor, antinuclear reacting gamma globulin and antithyroid antibody have also been obtained in asymptomatic members of the immediate family of a proband with Sjögren's syndrome [21].

How can we best approach an understanding of the striking phenomena noted: (1) overlapping of the symptoms and signs of the connective tissue diseases with each other, as well as with agammaglobulinemia, Sjögren's syndrome, and perhaps thyroiditis and others; (2) the familial occurrence of rheumatoid arthritis, lupus erythematosus and agammaglobulinemia; (3) the occurrence of connective tissue diseases in relatives of probands, often differing from that of the proband; and (4) the presence of a number of abnormal gamma globulin factors in the serum of asymptomatic relatives of patients with connective tissue diseases? The evidence seems strong that a common genetic abnormality links these diseases. The occurrence of isolated and specific gamma globulin abnormalities as the only expression of the defect in many persons, and the general evidence suggesting a hypersensitivity state in the connective tissue diseases suggest that the major site of the presumed genetically determined abnormality is the antibody synthesizing (reticuloendothelial) system.

Assuming a genetic abnormality, two possibilities may be considered. One is that this group of familial abnormalities is transmitted by a multifactor type of inheritance in which a number of linked genes participate. However, it appears more desirable to attempt to explain these abnormalities, instead, on the basis of a single genetic defect. It is, of course, difficult to

envisage a single biochemical abnormality which could bring about directly the variety of pathologic changes seen in the group of diseases under discussion. But, since these changes are in large part manifestations or consequences of inflammation of the connective tissue, it is necessary only that the underlying genetic abnormality be such as to permit the development of a more or less diffuse inflammatory reaction, the pattern of which would depend on the particular connective tissue constituents involved.

In view of the successful induction of thyroiditis in the rabbit by immunization with thyroid extract [22]; the induction [23] and subsequent transfer [24] of allergic encephalomyelitis in the rat by means of lymph node cells; the production of aspermatogenesis in the guinea pig by immunization with testicular tissue [25] and adrenalitis by injection of homologous adrenal gland [26], it appears reasonable to invoke an autoimmune reaction as a possible cause of this type of inflammatory response. If we accept this possibility, the type of pathologic change developing in the individual connective tissue diseases would presumably depend on the nature and number of autoantigens to which the patient became sensitive. The basic genetic error, however, need only be that the patient could become sensitive to one or a number of these antigens on the basis of an underlying genetically determined abnormality permitting an autoimmune response which would otherwise not occur.

As far as serum antibody is concerned, the postulated aberration would seem, as indicated by Fudenberg and co-workers [20], to result in hypergammaglobulinemia [27] under certain circumstances, in other circumstances in the as yet unexplained abnormal proteins of the rheumatoid factor type, and in still others in agammaglobulinemia. A number of facts appear also to implicate the delayed type of hypersensitivity reaction in the abnormal immunologic response postulated in the collagen diseases. Among these are the occurrence of connective tissue disease in patients with agammaglobulinemia, the failure to date to relate known serum factors such as the rheumatoid and L.E. factors to the etiology and pathogenesis of the diseases in which they occur, the apparent nonspecificity of known serum autoantibodies such as those present in disease of the thyroid [28], and the failure to effect passive transfer of thyroiditis [29] or rheumatoid arthritis [30] with

serum. The successful transfer of an autoimmune disease, allergic encephalomyelitis, in rats by means of lymph node cells [24] emphasizes the significant role of cellular "antibody." An abnormal potentiality for delayed hypersensitivity response to autoantigens would seem, therefore, to be worthy of consideration as a necessary part of the proposed genetic defect.

In what manner could a genetic defect predispose to the development of autoimmunity? This would depend on the mechanism accepted for the development of this type of immunity. An autoimmune response might occur as a result of one of three possible mechanisms: (1) excessive amounts of normal tissue constituents are liberated from tissue stores with the result that a normal immune mechanism is stimulated to synthesize autoantibody either of the immediate or delayed type; (2) altered tissue constituents are liberated from tissue stores and these stimulate a normal immune mechanism to synthesize autoantibody; or (3) the amount and character of tissue constituents liberated from tissue sources are normal, but the host response to these substances is abnormal with the result that autoantibody is produced. It is difficult to rule out any of these possibilities with complete certainty.

The first possibility could conceivably entail a genetically determined, generalized weakness of connective tissue basement membrane or similar supporting structure which would allow excessive amounts of antigen to be disseminated. There has been no evidence for this type of abnormality to date, however. It must be recognized, also, that the normal process of cell degradation constantly provides an abundance of potential antigen to the macrophages of the reticuloendothelial system to which no immune response occurs in the normal subject.

There is, to be sure, as pointed out by Medawar [31], a group of substances which are, presumably, potentially antigenic for the individual but are anatomically and physiologically isolated from the reticuloendothelial system and therefore do not ordinarily produce autoantibodies. Included in this category are nervous tissue, lens protein, spermatozoal antigen and thyroglobulin. An isoimmune response to all these tissues has been produced by active immunization.

Human thyroiditis and allergic encephalomyelitis may well represent disease states in which the anatomic barriers surrounding nerve and thyroid tissue antigens have been broken, with the resultant development of delayed hypersensitivity [24] as well as serum antibody. It is not possible, in the present state of our knowledge, to speculate fruitfully whether this type of autoimmunization is under genetic influence. It would appear, however, that autoimmunization resulting primarily from a breakdown of anatomic isolation would depend inherently on triggering stimuli of relatively incidental nature, such as trauma or infection, rather than on a genetic defect. Illustrative of the latter is the development of thyroiditis following mumps [32].

The second possible mechanism for autoimmune response mentioned, namely, that
altered constituents of normal tissue act as
autoantigens, has been considered by Lawrence
[33]. He has suggested that specific environmental factors may modify normal body constituents so that they become antigenic and lead
to the formation of antibodies which subsequently may attack the unmodified or native
antigen by cross reaction. It is difficult to see
how such a mechanism could be under genetic
control since it is *ipso facto* an environmental
phenomenon. Whether native body constituents
may undergo spontaneous modification and so
become antigenic is a matter of conjecture.

Most attractive as a mechanism for the development of autoimmunity which would be dependent on genetic influence is the last possibility mentioned, namely, that certain autoimmune reactions result from an inherent abnormality of host response. Current ideas about autoantibody formation derive much from the hypothesis of Burnet and Fenner [34] that the major immunologic adjustments in which the organism learns to recognize "self" from "non-self" take place in embryonic life. There is evidence that cellular transformations occur at this time which block the normal pathways of antibody production in response to antigens available to the embryo. Support for this concept was furnished by Medawar and his co-workers [35-38] who induced the development of tolerance to skin homografts by injection of living cells from donor strains into embryos of host strains of inbred animals. Tolerance was subsequently also induced by intravenous inoculation of newborn animals with living cells [39]. That the tolerance so produced continues only as long as antigen persists in the body is indicated by the work of

Smith and Bridges [40] who gave injections of large doses of bovine serum albumin to rabbits neonatally and found that the resulting unresponsiveness to this antigen disappeared after a period of time. This occurred at a time when the antigen was estimated to have disappeared from the body.

Burnet [41], in his clonal selection theory, has proposed that the capacity to produce a given antibody is a genetically determined quality of certain clones of mesenchymal cells, the function of the antigen being to stimulate cells of these clones to proliferation and antibody production. The central feature of the hypothesis is that contact of immunologically competent cells with corresponding antigen during embryonic life results in the elimination of these cells and, thereby, in tolerance.

Regardless of whether immune tolerance is produced by the mechanism proposed by Burnet, it is a fact, which is strongly supported by the experiments already referred to, that immunity to antigens is acquired during embryonic or neonatal life. It seems reasonable, therefore, to propose that the undesirable auto-immune reactions with which we are concerned may be a consequence of a genetically transmitted failure of a mechanism normally present for the acquisition of immune tolerance to normal body constituents during embryonic life.

Given a subject with the postulated immunogenetic fault of embryonic life which predisposes him to development of autoimmune responses, what would determine the actual occurrence of any given response in point of time? The presence of rheumatoid factor, L.E. factors, biologic false positive Wassermann antibody and possibly other abnormal gamma globulins in the serum in the absence of overt disease would suggest that serum "autoantibody" formation may long precede the development of symptoms-if the latter develop at all. In this there is a parallel with the latent biochemical defects seen in a number of hereditary diseases, such as the decreased levels of ceruloplasmin in Wilson's disease prior to the onset of symptoms. To some extent, as is common with known genetically determined disease, the factor of age alone may delay the time at which the occult abnormality asserts itself [42].

The frequently abrupt onset or exacerbation of symptoms in the connective tissue diseases, however, would seem to require a type of response more immediately related to the production of symptoms than that represented by known serum factors. Release of antigen responsible for this kind of response might be triggered by any of a number of possible stimuli, such as trauma in rheumatoid arthritis, sun exposure or pregnancy in S.L.E., tumors in polymyositis, as well as infection, drugs and possibly emotional stresses in the entire group.

Since the tendency to develop delayed hypersensitivity is somewhat decreased in patients with agammaglobulinemia [4], it may appear difficult to ascribe the frequent development of connective tissue diseases in patients with agammaglobulinemia to this phenomenon. The fact remains, however, that delayed hypersensitivity does occur in both the congenital and acquired types of agammaglobulinemia (really hypogammaglobulinemia) [4]. It may be no coincidence, also, that a defect in which antigens manifest a decreased capacity to effect the synthesis of antibody should be associated closely with a defect in which certain antigens may not be distinguished as isologous.

The impressive relationship between the agammaglobulinemic state on the one hand and a tendency to connective tissue disease and the presence of abnormal gamma globulins in blood relatives on the other suggests the possibility that the hypogammaglobulinemia and absence of plasma cells which occur in this condition might in fact be a consequence of an autoimmune reaction. Since, as previously mentioned, a number of autoantibody-like factors which react with intracellular substances have been described in patients with S.L.E., the possibility arises that an autoantibody to a critical intracellular constituent might be produced in agammaglobulinemic subjects which, when the necessary concentration of antibody had been achieved inside the cell, would result in the death of the plasma cell in which it was formed.

Helmreich, Kern and Eisen [43a] have offered evidence that there is an ordered arrangement of intracellular antibody in the plasma cell which tends to segregate this antibody in the cell sap. This raises the possibility that it is to a constituent of this cellular compartment that the antibody concerned might be directed. The mechanism suggested, however, faces the objection that virtually all clonal lines of plasma cells would have to produce this antibody in order to account for the absence of plasma cells and of almost all of the circulating gamma globulin observed in agammaglobulinemia.

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Assuming a genetic aberration permitting delayed type autoantibody formation to constitute the error responsible for the development of connective tissue disease, it is to be anticipated, as is common with hereditary diseases, that the abnormalities arising therefrom would be expressed to a variable degree. While minor expression might lead only to occult serologic abnormalities, at maximal expression on the other hand, one might in theory expect in the same subject an accumulation of all of the changes possible in rheumatoid arthritis, S.L.E., scleroderma and dermatomyositis, as a consequence of participation of a maximal number of antigens in the autoimmune response. A moderate degree of expression would be expected to give rise to the symptom complexes more commonly seen. This general idea has already been applied by Epstein [43b] to the connective tissue diseases from another point of view.

Statistically, the most common expression of this multifaceted genesis would be rheumatoid arthritis. It may perhaps seem difficult to reconcile this suggestion pertaining to patients as a group with intrafamilial observations such as that of Leonhardt [15] who observed three siblings in one family with S.L.E., since the latter phenomenon appears to be a relatively unique expression in one family of a multifaceted syndrome in which the rheumatoid picture is on the whole far more frequent. This may perhaps be explained by the fact that there is a known interfamilial variability in penetrance and expression of individual components of multifaceted syndromes of known hereditary character, such as Marfan's syndrome, apparently because of the influence of the genetic milieu [44] characteristic of individual families. This variability tends to bring out certain components over others within individual family groups.

It seems appropriate as a consequence of the point of view proposed, to regard the rheumatoid and L.E. factors as more or less independent immunologic responses. As pointed out previously, these proteins are not limited to the diseases with which they are commonly identified, but occur with other members of the connective tissue disease group. They have, in fact, been demonstrated in asymptomatic subjects. Evidence to date has not linked them to the etiology or pathogenesis of either rheumatoid arthritis or S.L.E., except perhaps for the development of arteritis in rheumatoid arthritis

[45] and hematoxylin bodies in S.L.E. They appear, therefore, to represent serologic abnormalities which occur concomitantly with connective tissue disease, but are not necessarily an essential part of it.

With regard to the rheumatoid factor, specifically, the point of view presented is compatible with the common observation of active synovitis in rheumatoid arthritis in the presence of low or absent titers of the factor, and conversely, with the presence of high titers in patients with minimal synovitis or burned out disease. It is also, as already mentioned, consistent with the occurrence of a rheumatoid-like arthritis, including subcutaneous nodules, in patients with agammaglobulinemia.

A special place in this picture may similarly be reserved for "arteritis," since this lesion is often qualitatively the same whether observed in its limited form, as in rheumatoid arthritis with neuropathy, or in its disseminated form, as in polyarteritis nodosa. Rheumatoid arteritis has in fact been reported to disseminate to full blown polyarteritis nodosa [46]. Arteritis also occurs as a significant pathologic change in the other connective tissue diseases.

These speculations are an attempt to explain a group of striking and seemingly related clinical, epidemiologic and serologic observations which have recently come to the fore in the connective tissue diseases. I have attempted to correlate them in terms of a single immunologic fault. Time may prove this fallacious but perhaps the point of view will prove fruitful in stimulating more purposefully directed investigation in this area.

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Postural Natriuresis and Urine Osmotic Concentration in Hydropenic Subjects*

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I has long been known that a change in posture from the erect to the supine position is accompanied by a transient increase in urine flow; in moderately hydrated subjects this diuresis reflects increased excretion of both water and solute, the latter principally sodium. (For literature see [30-32,45].) When it appeared to us that many studies, including some of our own, directed toward the elucidation of the control of salt and water balance may have been complicated by this postural diuresis, we undertook a more detailed examination of its nature, magnitude and duration. Because water diuresis and natriuresis can be independently evoked [16,41], and because both are observed during the diuresis of recumbency in moderately hydrated subjects, we elected to place our subjects in a more or less standard hydropenic state.

Emerging from this study are two conclusions: First, when the hydropenic, ambulatory subject assumes the recumbent position, the ensuing diuresis is primarily a natriuresis; the excretion of potassium and urea may be increased, but only secondarily, we believe, to the increased excretion of sodium. Secondly, during this diuresis the osmotic concentration of the urine remains constant, implying similar constancy in the medullary interstitium despite the fact that the quantity of solute-free water (T_{H₂O}) abstracted into the medulla increases with the urine flow. Accepting that the medullary hyperosmotic state is primarily established by sodium absorption out of the loop of Henle, the observed constancy of the urine osmotic pressure suggests that sodium transport in the loop is self-limited by a maximal interstitial sodium concentration or, what is more probable, by the concentration

gradient between the medullary interstitium and the urine in the loop. It is further suggested that during marked osmotic diuresis, when $T^{\rm e}_{\rm HaO}$ is substantially increased, this interstitial concentration, or concentration-gradient limitation with respect to sodium gives way to a maximal rate limitation, with the consequence that $T^{\rm e}_{\rm HaO}$ attains an approximately constant and maximal value ($Tm^{\rm e}_{\rm HaO}$).

METHODS

A single series of observations has been made on each of thirteen women subjects, who presented no evidence of cardiovascular-renal disease. These subjects ranged in age from twenty-four to forty-five years. They were selected from the wards of the Third (New York University) Medical Division of Bellevue Hospital, and had been eating the regular hospital diet. Female rather than male subjects were chosen because of the relatively greater ease in emptying the bladder. No subject was examined twice because of limited availability of "normal" subjects and we preferred, within our restricted opportunity, to examine the largest possible number of subjects.

No fluids were permitted for twenty-four hours preceding the test, and no infusions were administered during the test. On the morning of the observation the subject voided immediately on arising (this collection constitutes what is called herein the "night" specimen, indicated by N in Table 1), and was brought to the research unit (8:00 A.M.) after one and a half to two hours of free movement about the ward. Six subjects were given a single intramuscular injection of 10 units of vasopressin (Pitressin, Parke Davis No. 161) within the last thirty minutes of the ambulatory period. The response to change in posture in the subjects who received and in those who did not receive vasopressin was similar, and for that reason no distinction between them is made in the discussion.

Immediately after coming to the research unit the

^{*} From the Department of Physiology, New York University School of Medicine, New York, New York. This study was aided by a grant (H-1172) from the National Heart Institute of the National Institutes of Health. Part of this work was performed during tenure as Veterans Administration Clinical Investigator, Coral Gables, Florida.

RENAL FUNCTION IN NORMAL, HYDROPENIC SUBJECTS IN RESPONSE TO CHANGE IN POSTURE. THE FIRST SIX SUBJECTS RECEIVED PITRESSIN TABLE 1*

N	Subject, Sex and Surface Area	Speci- men	V (ml./min.)	Uosm (mOsm./ kg. H2O)	UNA UK (mEq./L.) (mEq./L.	UK (mEq./L.)	Uur (mM./L.)	Uosm	Uer Per	Cert	UosmV (µOsm./min.)	UNaV (µEq./min.)	UKV (µEq./min.)	Cosm (ml./min.)	T ⁶ _{H2O} (ml./min.)	Uosm (%)	Ukt Uosm (%)	Voem - Uurs
S.S. 6.90 1.00 6.90 4.00 <th< td=""><td>3. C., F</td><td>Z</td><td>:</td><td>1160</td><td>104</td><td>128</td><td>598</td><td></td><td>270</td><td>:</td><td>:</td><td>:</td><td>* * * *</td><td>* * *</td><td>* * *</td><td>16.7</td><td>20.4</td><td></td></th<>	3. C., F	Z	:	1160	104	128	598		270	:	:	:	* * * *	* * *	* * *	16.7	20.4	
SS 603 1070 62 240 575. 104 575. 104 575. 104 575. 104 575. 104 575. 104 575. 104 107 575. 104 107 575. 104 107 575. 104 107 575. 104 107 575. 104 107 575. 105. 107 575. 107	1.35	A		1140	6/	209	510		230			. [13.0	33.4	
SST 600 1970 59 256 473 577 167 166 643 99 164 227 167		65	653	1070	69	261	403		104	106	430	40	170	1.33	1 21	10 01	44.0	2.40
S4 633 930 51 250 432 153 165 78 888 83 158		83	009	1070	20	268	473		147	106	643	30	191	2.27	1.67	8 8	45.4	2.16
SSF -881 932 179 227 333 86 72 871 162 200 2.94 2.05 170 234 2.05 170 234 2.05 170 234 2.05 170 234 2.05 130 2.34 2.05 130 2.34 2.05 130 2.34 2.05 2.04 2.05 2.04 2.05		84	.633	930	51	250	428		105	78	588	32	158	2.09	1.46	10.3	48.9	1.82
National Color Nati		\$54	.881	932	79	227	378		98	72	821	89	200	2.94	2.06	16.0	44.4	2.02
N		00	0.1	930	011	107	3/0		00	6/	116	771	7117	3.50	2.43	23.0	39.4	2.03
National Color Nati	1. S., F	z.	•	728	202	19	286	2.58	135	0 0				:		51.1	15.7	
SS 5 350 978 1770 333 350 252 349 978 1770 978 1770 978 1770 978 1770 978 1770 978	1.55	A	360	138	150	101	304	2.62	190	* * *		. 0	* * *			37.6	25.3	
S.5. 4.67 900 178 156 326 102 420 83 773 1148 110 356 43.4 S.5. 1.80 855 195 115 226 102 102 102 102 102 103 114 2.32 114 2.32 114 2.32 115 245 200 112 102 661 1156 114 2.37 114 2.32 115 116 117 <t< td=""><td></td><td>S 22</td><td>380</td><td>918</td><td>170</td><td></td><td>333</td><td>3.00</td><td>262</td><td></td><td>348</td><td>50</td><td></td><td>1.10</td><td>0.74</td><td>34 3</td><td>:</td><td>2 10</td></t<>		S 22	380	918	170		333	3.00	262		348	50		1.10	0.74	34 3	:	2 10
S4 600 855 183 136 232 230 186 101 6512 110 82 1180		83	.467	006	178	156	366	3.16	222	102	420	83	73	1.48	1.01	36.6	31.1	1.91
SS 1800 928 195 126 245 2.09 120 661 156 101 2.32 1,34 4,34 4,40 114 2.32 1,55 4,47 1,40 100 114 2.32 1,55 4,47 1,40 100 114 2.31 2.97 1,52 4,47 1,40 100 156 3.76 4,63 1,40 100 156 100 256 3.76 4,40 100 6,64 1,40 6,64 1,40 6,64 1,40 6,64 1,40 6,64 1,40 1,		84	009	855	183	136	322	3.02	158	101	512	110	82	1.80	1.20	39.4	29.5	1.90
N		S5 S6	1.07	828	195	126	245	2.09	132	102	661 846	156	101	2.32	1.52	43.4	28.0	2.08
A 4.40 1140 156 102 556 3.76 443 4.40 68 44 1.61 1.61 S2 .420 10100 217 89 422 2.31 226 126 146 56 2.10 1.40 9.95 S3 .420 1010 227 89 422 2.31 1.86 1.46 56 2.10 1.46 59 3.95 S44 .604 1020 224 1.31 3.66 3.40 1.86 3.40 1.97 2.08 1.46 3.9 1.98 3.40 1.89 3.40 1.89 3.40 1.89 3.40 1.80 4.4 1.10 1.46 3.90 1.46 3.90 1.44 1.40 3.90 1.40 3.90 1.40 3.90 1.40 3.90 1.40 3.90 1.40 3.90 1.40 3.90 1.40 3.90 4.40 3.90 3.90 3.90 3.90 <td< td=""><td>F. B., F</td><td>Z</td><td></td><td>1230</td><td>115</td><td>101</td><td>630</td><td>4.07</td><td>200</td><td>:</td><td>:</td><td>* * *</td><td>:</td><td>* *</td><td></td><td>17.4</td><td>15.2</td><td></td></td<>	F. B., F	Z		1230	115	101	630	4.07	200	:	:	* * *	:	* *		17.4	15.2	
S1 440 1000 156 100 436 336 333 440 68 444 144 145 138 83 S2 400 1060 244 93 454 1.49 220 126 636 144 77 2.10 1.88 39.5 S44 1023 234 113 360 3.40 175 144 79 2.06 1.40 9.0 S5 847 1020 244 119 360 3.40 126 636 144 79 2.06 1.40 9.0 144 79 2.0 1.20 8.2 1.40 9.0 144 79 2.0 1.20 8.2 1.41 79 2.0 1.20 1.40 <td>1.57</td> <td>A</td> <td>_</td> <td>1140</td> <td>86</td> <td>102</td> <td>558</td> <td>3.76</td> <td>463</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>16.1</td> <td>16.6</td> <td></td>	1.57	A	_	1140	86	102	558	3.76	463							16.1	16.6	
S.S. -4.20 1010 241 99 452 91 37 140 0.96 39.5 SS4 .604 1020 244 131 360 3.99 175 118 619 141 56 2.10 1.50 42.1 93.5 3.5 3.5 3.6 3.6 3.40 180 181 2.08 107 2.88 2.10 1.50 42.1 3.5 3.5 3.6		SI		1000	156	100	396	3.30	303	* 1	440	89	44	1.45	1.01	28.8	18.5	2.03
S54 GOOD 1000 234 35 424 130 424 130 424 130 421 140 750 140 750 140 150 141 750 2.00 1.50 44.2 S54 .847 1020 234 116 306 3.40 150 118 863 208 107 2.88 42.03 44.2 150 44.2 120 120 44.2 103 44.2 103 100 100 118 114 70 2.88 13.9 100 44.2 100 140 100 140 100 140 100 140 100 140 100 140 100 140 100 140 100 140 100 140 100 140 100 140 100 140 100 140 100 100 100 100 100 100 100 100 100 100 100 100		25		1010	217	680	422	3.31	258	120	424	16	37	1.40	0.98	39.5	16.4	1.97
S5 1847 1020 246 124 102 3.40 150 118 663 141 141 141 150 3.40 150 118 663 218 167 2.88 2.03 44.2 150 160 170 2.88 2.03 44.2 150 160 178 160 2.72 119 266 3.42 149 126 144 212 98 2.82 1.99 46.0 S1 .31 1010 80 216 522 3.56 174 79 408 47 78 1.99 46.0 S2 .400 1020 118 194 470 363 61 47 78 1.36 1.99 46.0 S3 .400 1020 1140 428 3.39 149 80 593 93 98 1.99 46.0 1.30 1.90 1.90 1.90 1.90 1.90 1.30 1.90		83		1000	244	93	454	3,49	220	122	636	146	200	2.10	1.50	42.1	16.3	2.04
S5 .827 1020 257 119 306 3.42 126 844 212 98 2.82 1.94 48.4 S7 .787 1030 227 110 285 3.46 122 121 88 2.73 1.94 48.4 S1 .787 1030 272 110 285 3.46 122 316 25 68 2.73 1.94 48.4 S2 .400 1020 118 136 5.2 3.56 3.70 316 25 68 2.73 1.94 48.4 S3 .433 100 140 180 240 3.31 168 7.7 48.8 1.36 2.73 1.94 48.4 S4 .560 1020 140 180 440 3.31 168 7.7 48.4 1.35 2.8 1.4 3.9 48.4 1.10 1.9 48.4 48.4 1.2 1.3 2.2		241	_	1020	246	126	300	3.40	150	118	610	208	107	2.00	2.43	41.9	23.0	2.24
S7 787 1030 272 110 285 3.46 152 121 811 214 86 2.73 1.94 48.4 S1 .313 1010 180 42 198 5.52 3.27 315 316 2.5 68 1.05 0.74 14.9 S2 .433 1000 140 180 426 3.20 1.04 78 1.36 0.74 14.9 S3 .433 1000 140 180 426 3.30 184 79 408 47 78 1.36 21.5 <td></td> <td>86</td> <td></td> <td>1020</td> <td>257</td> <td>119</td> <td>306</td> <td>3.42</td> <td>149</td> <td>126</td> <td>844</td> <td>212</td> <td>98</td> <td>2.82</td> <td>1.99</td> <td>46.0</td> <td>21.6</td> <td>2.44</td>		86		1020	257	119	306	3.42	149	126	844	212	98	2.82	1.99	46.0	21.6	2.44
A 980 42 198 532 3.27 315 316 25 68 1.05 0.74 S2 .400 1020 118 194 570 3.50 7.0 316 25 68 1.05 0.74 S3 .433 1000 140 180 47 78 47 78 1.36 0.06 S4 .580 1020 140 180 47 78 1.36 0.06 S5 .580 1021 160 170 428 3.39 149 80 593 93 98 1.97 1.39 S6 .342 1061 170 428 3.39 149 80 593 93 98 1.99 1.39 S5 .350 1061 170 428 3.39 14 86 571 91 1.00 1.89 1.39 S7 .30 110 <		S7		1030	272	110	285	3.46	152	121	811	214	98	2.73	1.94	48.4	19.6	2.55
S1 313 1010 80 216 522 3.36 270 316 25 68 1.05 0.74 S2 .400 1020 118 194 570 3.36 174 79 408 47 78 1.05 0.04 S3 .430 1020 140 180 440 3.36 149 80 593 93 98 1.95 1.36 0.06 S4 .580 1020 162 178 460 3.38 154 86 571 91 100 1.85 1.36 1.39 S5 .560 1020 162 178 460 3.38 149 80 571 91 100 1.89 1.39 S6 .342 18 3.53 21 363 65 48 1.20 88 1.91 1.90 1.93 S1 .37 18 23 21	E. S., F	4	:	980	42	198	5.52		315	:			:	:	:	7.8		
S2 .400 1020 118 194 570 3.50 174 79 408 47 78 1.36 0.96 S3 .433 1000 140 180 440 3.33 168 71 433 61 78 1.35 1.02 S4 .580 10201 160 170 428 3.33 149 80 593 98 1.97 1.02 S5 .560 10201 160 178 460 3.38 154 86 571 91 100 1.89 1.39 SA .342 160 206 178 460 3.38 171 1.20 0.86 S1 .337 1060 206 187 2.96 3.86 211 1.20 0.86 S1 .337 160 206 187 3.7 3.4 1.7 87 556 116 86 1.20 1.8<	1.71	S	.313	1010	80	216	522		270		316	25	89	1.05	0.74	14.9	_	
S3 .433 1000 140 180 440 3.33 168 71 433 61 78 1.45 1.02 S4 .580 1021 160 170 428 3.39 149 80 593 93 98 1.02 1.39 S5 .560 1020 162 178 428 3.39 149 80 571 91 100 1.89 1.39 S6 .342 160 451 3.35 181 76 363 65 48 1.20 0.86 N 1060 206 187 2.86 211 1.20 0.89 1.39 S2 .533 1060 218 162 3.86 211 341 341 1.45 8.8 1.45 1.46 1.46 <		S2	.400	1020	118	194	570		174	79	408	47	78	1.36	96.0	21.5	_	
S4 .580 1021 160 170 428 3.39 149 80 593 93 98 1.97 139 S5 .560 1020 162 178 460 3.38 154 86 571 91 100 1.89 1.33 S6 .342 178 460 3.38 164 1.20 1.89 1.33 A 1060 206 187 2.39 211 <td></td> <td>83</td> <td>.433</td> <td>1000</td> <td>140</td> <td>180</td> <td>440</td> <td></td> <td>168</td> <td>71</td> <td>433</td> <td>61</td> <td>78</td> <td>1.45</td> <td>1.02</td> <td>26 0</td> <td>32.9</td> <td>1.90</td>		83	.433	1000	140	180	440		168	71	433	61	78	1.45	1.02	26 0	32.9	1.90
S5 .560 1020 162 178 460 3.38 154 86 571 91 100 1.89 1.33 S6 .342 1061 190 140 451 3.35 183 76 363 65 48 1.20 0.86 N 1120 165 120 532 3.93 211 341 48 1.20 0.86 S1 .307 1110 178 209 3.46 211 341 55 64 1.20 0.86 S2 .533 1060 218 209 3.49 1.7 341 341 341 341 341 1.14 341 341 <td></td> <td>S4</td> <td>.580</td> <td>1021</td> <td>160</td> <td>170</td> <td>428</td> <td></td> <td>149</td> <td>80</td> <td>593</td> <td>93</td> <td>98</td> <td>1.97</td> <td>1.39</td> <td>29.0</td> <td>-</td> <td></td>		S4	.580	1021	160	170	428		149	80	593	93	98	1.97	1.39	29.0	-	
S6 .342 1061 190 140 451 3.35 183 76 363 65 48 1.20 0.86 N 1120 165 120 532 3.93 211		82	.560	1020	162	178	460		154	98	571	91	100	1.89	1.33	29.4	_	
N 1120 165 120 532 3.93 211 <td></td> <td>98</td> <td>.342</td> <td>1001</td> <td>190</td> <td>140</td> <td>451</td> <td></td> <td>183</td> <td>16</td> <td>363</td> <td>99</td> <td>48</td> <td>1.20</td> <td>0.86</td> <td>33.0</td> <td></td> <td></td>		98	.342	1001	190	140	451		183	16	363	99	48	1.20	0.86	33.0		
A 1060 206 187 296 3.86 211 341 55 64 1.20 0.89 S1 .307 1110 178 209 349 3.90 244 341 55 64 1.20 0.89 S2 .533 1960 218 162 246 173 87 555 139 72 1.98 1.45 S4 .633 980 268 114 292 3.49 147 87 555 139 72 2.19 1.55 S5 .773 954 228 3.49 147 87 555 139 72 2.19 1.55 S6 .773 954 228 3.40 115 85 693 210 72 2.19 1.75 S7 .860 945 320 78 3.40 106 84 753 240 71 2.88	M. K., F	Z		1120	165	120	532	3.93	211	0 0			0 0		•	27.3		
S1 .307 1110 178 209 349 3.90 244 341 55 64 1.20 0.89 S2 .533 1060 218 162 346 3.86 173 87 565 116 86 1.98 1.45 S3 .560 991 248 130 285 3.46 187 565 116 86 1.95 1.45 S4 .633 980 268 114 292 3.46 187 565 116 86 1.95 1.95 1.95 1.95 1.39 1.45 1.55 1.39 1.45 1.55 1.39 1.45 1.55 1.39 1.45 86 1.93 1.72 2.48 1.75 1.55 1.55 1.75 2.48 1.75 2.48 1.75 2.48 1.75 2.48 1.75 2.48 1.75 2.48 1.75 2.48 1.75 2.48 1.75 2.48	1.35	Y		1060	206	187	296	3.86	211				:	:		35.4		
S2 .533 1060 218 162 346 3.86 173 87 565 116 86 1.98 1.45 S3 .560 991 248 130 285 3.49 147 87 555 119 72 1.98 1.45 S4 .633 980 268 130 292 3.46 135 84 620 169 72 2.19 1.55 S5 .773 954 286 98 232 3.40 166 84 753 240 72 2.19 1.75 S6 .773 956 301 90 243 3.40 106 84 753 240 71 2.70 1.90 S7 .860 945 320 78 3.41 106 91 835 292 53 3.00 2.12 N 936 53 126 254 3.04 2.74		S1		1110	178	209	349	3.90	244		341	55	64	1.20	0.89	29.7		
S3 .560 991 248 130 285 3.49 147 87 555 139 73 1.95 1.39 S4 .633 980 268 114 292 3.46 135 84 620 169 72 2.19 1.55 S5 .733 954 286 301 90 243 3.40 106 84 753 240 77 2.79 1.75 S6 .793 956 301 90 243 3.40 106 84 753 240 77 2.79 1.90 S7 .850 945 320 276 3.39 104 86 803 271 66 2.88 2.03 S8 .880 950 332 60 228 3.41 106 91 835 292 53 3.00 2.12 A 936 53 126 274 342 <t< td=""><td></td><td>\$2</td><td></td><td>1060</td><td>218</td><td>162</td><td>346</td><td>3.86</td><td>173</td><td>87</td><td>565</td><td>116</td><td>98</td><td>1.98</td><td>1.45</td><td>37.8</td><td></td><td></td></t<>		\$2		1060	218	162	346	3.86	173	87	565	116	98	1.98	1.45	37.8		
S4 .633 980 268 114 292 3.46 135 84 620 169 72 2.19 1.55 S5 .733 954 286 98 232 3.40 115 85 693 210 72 2.48 1.75 S6 .793 950 301 90 243 3.40 106 84 753 240 71 2.70 1.90 S7 .850 945 320 78 216 3.39 104 86 803 271 66 2.88 2.03 S8 .860 950 332 60 228 3.41 106 91 835 292 53 3.00 2.12 N 837 18 256 574 342 A 837 18 256 274 342		83		991	248	130	285	3.49	147	87	555	139	73	1.95	1.39	45.8	_	
S5 ./33 954 280 98 232 3.40 115 85 693 210 72 2.48 1.75 S6 ./73 950 301 90 243 3.40 106 84 753 240 71 2.70 1.90 S7 .850 945 320 78 216 3.39 104 86 803 271 66 2.88 2.03 S8 .880 950 332 60 228 3.41 106 91 835 292 53 3.00 2.12 N 837 18 256 274 342		\$ 2		980	268	114	292	3.46	135	40	620	169	72	2.19	1.55	50.0		
Sylvariant		200		954	286	800	232	3.40	115	82	693	210	72	2.48	1.75	54.9	_	
S8 .880 950 332 60 228 3.41 106 91 835 292 53 3.00 2.12 N 936 53 126 549 3.06 291		200	_	930	300	30	243	3.40	100	84	/53	240	11	2.70	1.90	20.0	_	
N 936 53 126 549 3.06 291 837 18 256 278 2.74 342 828 10 256 278 2.74 342		80.00		950	332	09	228	3.41	106	91	83.5	292	53	3.00	2.12	63.6	11.8	
N 936 53 126 549 3.06 291 10												3	1					
24 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	R. G., F	Z	•	936	50.00	126	549		291	:	:	:	:		•	10.6	24.8	
7 T T T T T T T T T T T T T T T T T T T	1.40	c v	200	828	10	244	328		246		773	: "			0 34	0.0	_	

Table 1 (Continued)

Subject, Sex and Surface Area		1.54 1.54	A. J., F. 1.68	S. R., F 1.67	M. C., F 1.62	M. Ma., F	A. G., F 1.67
Speci- men	\$2† \$3† \$4	S S S S S S S S S S S S S S S S S S S	S S S S S S S S S S S S S S S S S S S	S24 S34 S4 S4	S S S S S S S S S S S S S S S S S S S	SS	Zezs
v (ml/min.)	.414				.500 .587 .700 .433		347
Uosm (mOsm./ kg. HrO)	824 886 900	936 900 972 918 855 870 900 900	1170 1120 1170 1201 1200 1099 1110	1060 1100 1030 1009 995	945 936 918 900 864 873	927 1035 1134 1116 1044 1071 1107	1044
UNa (mEq./L.)	12 56 102	84 64 116 159 164 169 173	184 234 224 260 274 302	166 159 184 229 239 240	166 168 175 172 171	159 204 226 233 248 256 277 295	146
UK (mEq./L.)	246 250 222	98 124 127 102 88 101 112	100 1112 121 115 110 101 90	72 101 103 90 91	178 171 176 180 189	88 149 126 105 94 95 1103	76 67 22 72
Uur (mM./L.)	382 381 351	433 399 425 399 372 352 352 379 452	555 462 475 509 484 386 376	474 439 396 367 311	111111	:::::::	635 621 657
Uosm	2.69 2.86 2.91	3.32 3.45 3.26 3.04 3.09 3.17 3.22	3.94 4.04 4.04 3.78 3.78	3.72 3.86 3.62 3.55 3.54	3.35 3.25 3.20 3.20 3.10	3.32 4.05 4.05 3.72 3.84 3.98 4.05	3.54
Uer Per	243 205 190	332 439 376 231 137 125 114 129	301 316 316 270 270 211 182 180	326 382 298 232 209 190	269 251 237 211 222 206	252 208 246 184 193 192 166 228	252 252 261
Cert	80 96 91	132 109 99 96	65 76 91 91 98	123:::	133	96 102 114 116 98	: : ; ;
UosmV (µOsm./min.)	341 395 432	324 324 569 700 724 731 702	202 320 352 352 528 618		468 539 630 374 276	452 452 596 656 636 476	364
U _{Na} V (µEq./min.)	2.54 4.9	39 98 135 136 137 137	39 62 76 131 181	75	84 103 120 74 53	90 118 126 157 159	67
UKV (#Eq./min.)	102 112 107		54 33 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	4 4 4 6 	86 103 126 82 62		
Cosm (ml./min.)	1.11 1.28 1.40	2.02 2.02 2.48 2.57 2.58 2.47 2.00	0.68 1.08 1.18 1.79 2.00	1.47	1.66 1.91 2.24 1.32 0.98	2.03 2.03 2.14 2.35 1.70	1.24
$T_{\rm HzO}^{\rm c}$ (ml./min.)	0.70 0.83 0.92	0.82 1.40 1.66 1.74 1.77 1.69	0.51 0.81 0.89 1.31	1.06	1.16 1.32 1.54 0.89 0.66	1.22	0.89
Unai Uosm (%)	2.8	16.8 13.4 22.2 31.1 35.5 34.9 34.8 35.6	29.0 38.4 35.2 35.2 35.9 39.6 47.4 49.8	29.0 26.8 32.8 41.6 44.0	32.5 32.5 35.4 35.4 35.7	31.8 36.8 36.8 38.2 43.6 43.7 45.7	19.0 24.8 29.1
Uki Uosm (%)	54.4		18.5 19.1 17.7 16.2 18.7 16.8	12.7 17.0 18.5 16.4 17.0	34.5 33.4 35.1 36.6 40.1	26.4 20.6 20.6 17.3 16.8 16.5 18.2	13.6
Uosm - Uur Posm - Pur	1.46	2.2.2.1.88 1.88 1.94 1.88	2.37 2.37 2.46 2.54 2.54	2.24	11:11:	11111111	1.37

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RECEIVED PITRESSIN SUBJECTS SIX FIRST THE IN POSTURE. RESPONSE TO CHANGE Table 1 (Continued) HYDROPENIC SUBJECTS IN NORMAL, Z FUNCTION RENAL

Postu	ral Natriuresis and
$rac{U_{ m osm}-U_{ m ur}}{P_{ m osm}-P_{ m ur}}$	1.62 1.62 1.93 1.93 2.00 2.00 2.10
UKi Uosm (%)	13.4 14.5 13.7 20.5 30.0 31.9 34.8 37.8 37.4 34.4
UNas Uosm (%)	36.4 41.8 41.8 22.7 22.7 26.2 26.8 28.1 28.0 27.8 31.2
Te TH2O (ml./min.)	1.50 1.17 1.29 2.03 1.67 1.56 1.31 1.00 0.84
Cosm (ml./min.)	2.13 1.73 3.02 2.34 1.97 1.49
UkV µEq./min.)	444 0 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4
UNaV (µEq./min.) (123 117 117 80 130 107 88 69
UosmV (µOsm./min.)	626 515 515 761 761 741 7446 368
Cert	102 102 102 103 103 103 103 103 103 103 103 103 103
Uer Per	185 162 280 214 143 107 103 119 119
Uosm	3.40 3.42 3.42 3.33 3.21 3.06 2.91 2.94 2.97
Uur (mM./L.)	551 452 625 625 517 425 359 306 312 302 302
Uk (mEq./L.)	71 72 76 111 158 160 160 182 182 182
UNA (mEq./L.)	196 212 212 106 122 132 133 133 133 133
Uosm (mOsm./ kg. H2O)	999 930 1026 999 963 918 873 882 891 900
V (ml./min.)	.627 .554 .987 .807 .660 .495
Speci- men	SS
Subject, Sex and Surface Area	1.37

Norre: N indicates night specimen; A indicates ambulatory specimen; S1, S2, S3, etc. indicate consecutive urine collection periods in the supine position, each fifteen minutes in length except where indicalculated as described in the text, ent positions. Smoothed endogenous creatinine clearance of Non-urea osmotic U/P ratio for all recumber all recumb ratio for U/P * Data not corrected for surface area.

† Thirty-minute urine collection period.

subject assumed the supine position without a pillow. The bladder was catheterized and emptied by means of repeated air wash-out and the catheter left in place. The urine collected at this time was designated the "ambulatory" specimen (indicated by A in Table 1). The time from lying down to collection of the ambulatory specimen was in all instances less than ten minutes. With few exceptions, urine was thereafter collected at fifteen minute intervals for one to two hours (S1, S2, etc. in Table 1). Observations were arbitrarily discontinued after diuresis had apparently reached a peak or, if no peak occurred, when the urine flow had stabilized at what appeared to be a maximal rate. Because of the oliguric state, extreme care was exercised in emptying the bladder and in timing all urine collection periods.

Fifteen milliliters of blood were collected from an antecubital vein in a heparinized syringe during the first recumbent period, and every subsequent thirty to forty minutes throughout the test. Blood samples were centrifuged immediately and the plasma removed and stored in stoppered plastic tubes immediately after collection.

Osmolal concentration of plasma and urine was determined within three hours after completion of each study by means of a Johlin freezing-point apparatus and the thermistor and bridge-null-point-detector unit of Bowman, Trantham and Caulfield [3] or by the Fiske osmometer. For other analyses, plasma and urine were refrigerated (but not frozen) within one hour after completion of the test. Sodium and potassium were determined by flame photometry with lithium as an internal standard and endogenous creatinine chromogen was determined by the method of Brod and Sirota [5]. Urine urea plus ammonia was determined in eleven subjects within twenty-four hours on refrigerated samples by the method of Seligson and Seligson [38].

Such changes as were observed in plasma concentrations of sodium, potassium, urea or endogenous creatinine chromogen, and in plasma osmolal concentration, during the test were marginal and not of a magnitude to affect the interpretation of the derived data.

Unfortunately, the possible significance of our results was not fully appreciated until after completion of the study, and we regret that we did not include urine ammonia, chloride, sulfate, phosphate and total water in our analytical procedures. However, we believe that errors introduced by the omission of these data do not jeopardize our conclusions.

RESULTS

Table I gives the observed and derived data relative to the night specimen (N), the ambulatory specimen (A), and specimens collected after the assumption of the supine position (S). The rate of urine formation in the overnight and ambulatory specimens was not determined.

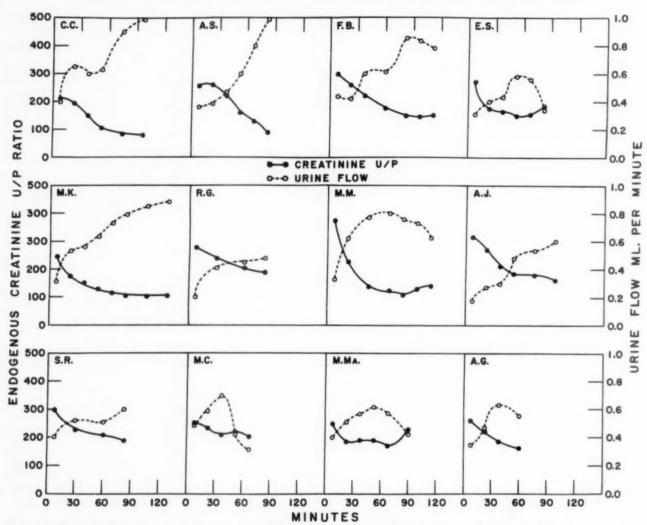


Fig. 1. Sequential changes in urine flow and endogenous creatinine U/P ratio after ambulatory subjects assume the supine position.

Urine flow. The urine flow (V) increased in all thirteen subjects; this increase was generally evident in the second fifteen minute period after lying down, as shown in Figure 1. The duration of the diuretic response was highly variable, but in some subjects (C. C., A. S., M. K. and A. J.) the urine flow was apparently still increasing at ninety minutes. As between the first supine period and the period in which V was maximal, the average increase for all subjects was 0.39 ml. per minute (range 0.19 to 0.71). This increase in V is small, but since all urine samples have a high osmotic U/P ratio, greater physiologic significance is to be attached to changes in the osmotic clearance (Cosm) and medullary water reabsorption (T_{H2O}) than to the urine flow itself.

Osmotic clearance. In moderately hydrated subjects, as we have noted, postural diuresis evokes some degree of water diuresis with a

consequent decrease in urine osmotic pressure. However, in our hydropenic subjects, whether or not Pitressin was received, the diuresis was a solute diuresis characterized by a constant urine osmotic pressure (U_{OSM}). (Table 1.) (Statistical analysis of the osmotic U/P ratio will be presented later.) Since the plasma osmotic pressure (P_{OSM}) remains constant, it follows that the osmotic clearance, C_{OSM} (= $\frac{U_{OSM}V}{P_{OSM}}$), increases in direct proportion to V, as shown in Figure 2.* Conversely, the linearity of the data

*In the definition of C_{OSM} as given here (and in equation 1) V should designate the excretion of water in grams per minu*e, in order for it to be commensurate with U_{OSM} and P_{OSM} , which are measured in millimols per kilogram of water. Strictly speaking, C_{OSM} as calculated here is neither an osmolar nor osmolal clearance, and consequently we will refer to it by the ambiguous term "osmotic clearance."

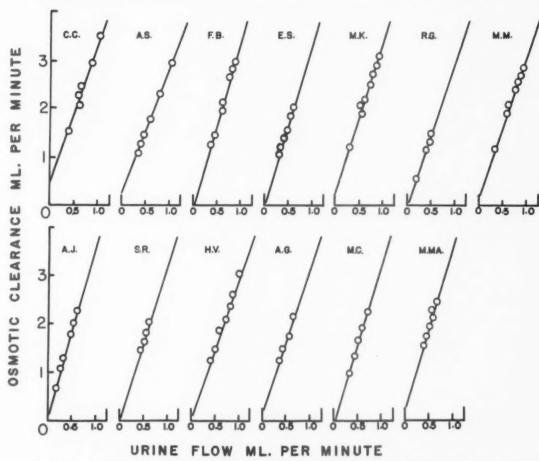


Fig. 2. Relation between osmotic clearance (C_{OSM}) and urine flow in ambulatory subjects during supine diuresis.

in Figure 2 relating C_{OSM} to V is an indication of the constancy of U_{OSM}/P_{OSM} (and hence U_{OSM}) in each subject. As between the first period in the supine position and the period in which C_{OSM} was maximal, the average increase in this term was 1.28 ml. per minute (range 0.55 to 1.97).

 $T_{H_2O}^c$. Because of the high osmotic U/P ratio, $T_{H_2O}^c$ increased more rapidly than V: as between the first supine period and the period in which $T_{H_2O}^c$ was maximal, the average increase in $T_{H_2O}^c$ was 0.83 ml. per minute (range 0.38 to 1.32).

Endogenous Creatinine U/P Ratio. In general, the creatinine U/P ratio in any one subject varied inversely with the osmotic clearance, or—since the osmotic U/P ratio is constant—inversely with V, as shown in Figure 1. The significance of this fact will be discussed later.

Sodium. Of the osmotically important constituents of the urine, sodium (with its attendant anions) is, we think, the most significant in respect to the phenomenon of postural diuresis.

In the supine position the urine sodium concentration, U_{Na}, increased in all subjects except two (M. C. and H. V.). (H. V. reacted anomalously in other respects and is not included in Figures 1 and 3.) The greatest value of U_{Na} frequently coincided with the greatest value of V as shown in eight subjects (C. C., A. S., F. B., M. K., R. G., A. J., A. G. and S. R.). Consequently sodium excretion (U_{Na}V) increased with V until the urine flow had stabilized or started to decrease. As between the first supine period and the period in which U_{Na}V was maximal, the average increase in this term was 108 μEq. per minute (range 47 to 237).

The sodium osmotic fraction* (i.e., the con-

* In the calculation of the contribution which sodium, potassium and urea individually make to the total osmotic concentration of the urine, molar concentrations (milliequivalents per liter) have again been substituted for molal concentrations (milliequivalents per kilogram of water). Ammonia is not distinguished from urea, although in more recent studies of this type ammonia constitutes less than 3 per cent of urea plus ammonia. For sodium and potassium, the osmotic coefficients (i) of the

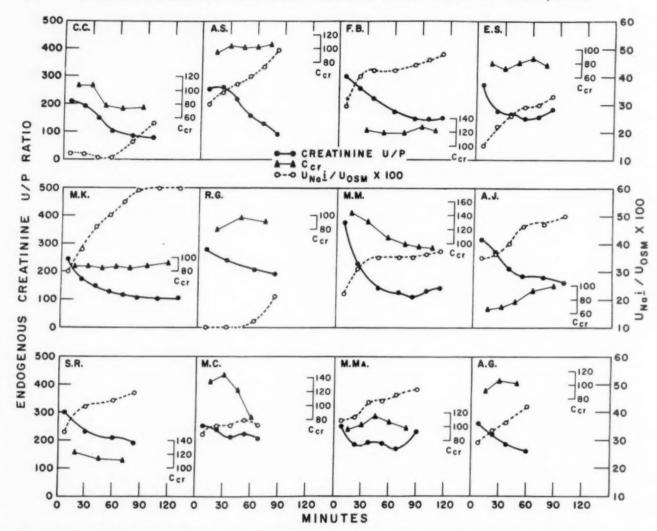


Fig. 3. Sequential changes in urine sodium osmotic fraction, endogenous creatinine U/P ratio, and endogenous creatine clearance after ambulatory subjects assume the supine position. To reduce emptying errors, a "smoothed" creatinine clearance was calculated by averaging successive pairs of values for V and creatinine U/P ratio. The consistent increase in the urine sodium osmotic fraction indicates that diuresis is related to increased excretion of sodium.

tribution which sodium salts make to the total osmotic concentration) in the urine, calculated as $U_{Na}i/U_{OSM}$, was frequently higher in the (morning) ambulatory specimen (A) than in the overnight specimen (N), as might be ex-

corresponding molal concentrations of NaCl and KCl have been interpolated [17]; for urea, i has been taken as 1. Where the use of molal concentrations gives low values for the fractional contribution of each solute to U_{OSM}, a larger error of opposite sign has been introduced by neglect of the fact that sodium and potassium are partly paired with (undetermined) divalent anions, sulfate or phosphate, which have a substantially lower osmotic coefficient than does NaCl. If it is supposed that increased sodium excretion represents chloride (rather than sulfate or phosphate), the relative increase in chloride excretion would be even larger than the data on U_{Na}V indicate, because the sodium chloride osmotic fraction at lower flows would be less than is indicated by total sodium.

pected from the diurnal cycle in sodium excretion. In only six subjects did this fraction increase between the ambulatory specimen and the first supine specimen, but in successive samples collected in the supine position the sodium osmotic fraction increased to some extent in every subject; frequently, as shown in five subjects (A. S., F. B., E. S., M. K., A. J.), this increase was very striking. With few exceptions, the sodium osmotic fraction and the creatinine U/P ratio varied inversely, as shown in Figure 3.

The concentration of potassium in the urine generally decreased with increasing urine flow in the supine position, in marked contrast to the increasing concentration of sodium. The osmotic contributions of the two cations are roughly inversely related, as

shown in the mass graph of Figure 4. Despite decreasing concentration, potassium excretion (UKV) increased to some extent in all subjects except one (M. K.), in whom an increase was evident only in the second supine period; the average increase (including M. K.) from first period to peak was 42.7 μEq. per minute (range 8.6 to 104).

The excretion of urea was followed in only eleven subjects. The urea osmotic fraction, like the potassium osmotic fraction, shows wide variations between different subjects, reflecting differences in nitrogen, sodium and potassium balance. The urine urea concentration (UUR) and the urea osmotic fraction (U_{UR}) decreased in most subjects between the night Uosm and ambulatory specimen, as might be expected from

a postprandial decrease in urea production and/or the diurnal rhythm in electrolyte excretion.

Except in one subject (R. G.), both the urea concentration and urea osmotic fraction decreased with increasing urine flow in the supine position. But because the increase in V outweighs the decrease in UUR, UURV increased in all eleven subjects, the average increase being 116 μ M. per minute (range 32

Primacy of Increased Sodium Excretion. It seems clear that the primary factor in postural diuresis is the increased excretion of sodium, indicated by the increase in urine sodium concentration (U_{Na}), sodium excretion (U_{Na}V), and sodium osmotic fraction (U_{Na}i/U_{OSM}), and that other changes in urine composition are secondary to this natriuresis. Despite increasing T_{H2O}, increasing excretion of sodium leads to increasing urine flow and reduction of the endogenous creatinine U/P ratio (Figs. 1 and 3). The increased excretion of potassium (UKV) may reflect stimulation of potassium secretion or, more plausibly, increased availability of sodium to the distal Na: K exchange mechanism. (Thomas [45,46] has shown that changing from the upright to the recumbent position decreases the excretion of H⁺, an observation consonant with either interpretation.) The increase in urea excretion may be related to the following two circumstances: first, in consequence of the increased excretion of sodium and potassium (with osmotically obligated water), the concentration of urea (like that of creatinine) in the collecting-duct urine is decreased, thereby reducing the diffusion of urea out of the duct [19,23]; and secondly, the extent of urea diffusion out of the duct may be reduced by the increase in velocity of urine flow through the duct.

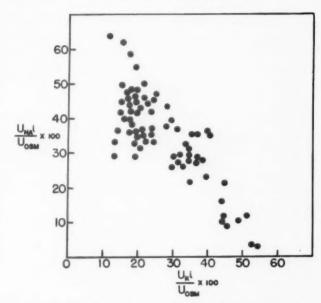


Fig. 4. Mass plot showing the general inverse relation between the sodium and potassium osmotic fractions in the urine during postural diuresis.

Osmotic U/P Ratio. Beyond the phenomenon of natriuresis, the most notable feature in our data is the approximate constancy, in any one subject, of the urine osmotic concentration during the diuresis induced by the supine position. (Table 1.) Since Posm remains essentially constant, it follows that the osmotic clearance, $C_{OSM} \left(= \frac{U_{OSM}V}{P_{OSM}} \right)$, is linearly related to V, as

shown in Figure 2 In analyzing this relationship mathematically, it is inappropriate to calculate a correlation coefficient (r) between $\frac{U_{OSM}V}{P_{OSM}}$ and V directly

because the variable (V) occurs in both terms and hence introduces simultaneous and correlated errors. A valid correlation coefficient can, however, be calculated, as suggested by Boyarsky and Smith [4], by treating the relation between $\frac{U_{OSM}V}{P_{OSM}}$ and V as an apparently linear

(1)
$$\frac{U_{\text{OSM}}V}{P_{\text{OSM}}} = aV + b$$
(2)
$$\frac{U_{\text{OSM}}}{P_{\text{OSM}}} = a + b \frac{1}{V}$$

one, and writing:

(2)
$$\frac{U_{OSM}}{P_{OSM}} = a + b \frac{1}{V}$$

In equation 2, b is the slope of the projected line, and a is the value of the ordinate intercept calculated by the method of least squares [43]. If the osmotic U/P ratio is in fact constant, the

TABLE II STATISTICAL ANALYSES OF URINE OSMOTIC PRESSURE AND URINE FLOW

Subject	Equation 1 Regression of C_{OSM} on V				Equation 2 Regression of $\frac{U_{OSM}}{P_{OSM}}$ on $\frac{1}{V}$				
Subject	Regression Coefficient a	Ordinate Intercept	Correlation Coefficient	p Value	Regression Coefficient b	Ordinate Intercept a	Correlation Coefficient	p Value	
C. C.	2.84	0.48	0.9717	<0.001	0.32	3.06	0.6840	>0.10	
A. S.	2.59	0.23	0.9960	< 0.001	0.20	2.65	0.8264	>0.02	
F. B.	3.45	-0.03	0.9858	< 0.001	-0.11	3.57	-0.7336	>0.05	
E. S.	3.36	0.01	0.9999	< 0.001	-0.01	3.42	-0.0730	>0.10	
M. K.	3.09	0.26	0.9999	< 0.001	0.26	3.10	0.8518	< 0.01	
R. G.	2.98	-0.06	0.9804	< 0.01	-0.05	2.94	-0.6183	>0.10	
M. M.	2.84	0.22	0.9999	< 0.001	0.19	2.90	0.9454	< 0.01	
A. J.	3.60	0.09	0.9999	< 0.001	0.06	3.69	0.6944	>0.05	
S. R.	3.31	-0.09	0.9960	< 0.001	0.14	3.24	0.5441	>0.10	
M. C.	3.39	-0.10	0.9999	< 0.001	-0.09	3.38	-0.5866	>0.10	
M. Ma.	3.37	0.29	0.9804	< 0.001	0.27	3.42	0.7456	>0.05	
A. G.	3.00	0.20	0.9909	< 0.01	0.26	2.84	0.6699	>0.10	
I. V.	2.89	0.09	0.9941	<0.001	0.09	2.88	0.4684	>0.10	
Mean	3.13	0.12			0.12	3.16			

slope or regression coefficient, b, of the projected line will be zero, and the correlation coefficient, r, for linear regression of $\frac{U_{OSM}}{P_{OSM}}$ on $\frac{1}{V}$ will not be significantly different from zero. (It may be noted that, in equation 2, a perfect zero correlation between $\frac{U_{OSM}}{P_{OSM}}$ and $\frac{1}{V}$ will be reflected by a correlation coefficient, r, of zero, while with perfect positive or negative correlation, r will approach plus 1 or minus 1, respectively; r values between zero and plus 1 or minus 1 indicate degrees of correlation which may or may not be statistically significant. Values of p greater than 0.01 are insignificant, and in such a case the regression coefficient, p, is not meaningful.)

Statistical analysis of our data by equation 2 (Table II), shows that the correlation coefficient between $\frac{U_{\rm OSM}}{P_{\rm OSM}}$ and $\frac{1}{V}$ is not significantly different from zero (p > 0.01) in eleven of thirteen subjects (the exceptions being M. K. and M. M., where p < 0.01); i.e., $C_{\rm OSM}$ has a significantly high linear correlation with V.

The average intercept, a, in equation 2 is 3.16 and the average slope, b, is 0.12; inserting these

values in equation 2 gives an average osmotic U/P ratio of 3.28, with a range (calculated separately for each subject) of 2.85 to 3.75.

Alternatively, the data have also been ana-

lyzed by the original method of Zak, Brun and Smith [57], wherein the slope and correlation coefficient are calculated directly from and V. (This direct calculation constitutes a physiologically valid procedure since Cosm could in theory be determined without reference to urine volume by measuring the renal A-V difference in plasma osmotic pressure and the concurrent renal plasma flow.) This method reveals near perfect positive correlation in all subjects (including M. K. and M. M.), as shown in Table II. At least under the circumstances of this study, as in the studies of Giebisch and Lozano [11], the presence of V on both sides of equation 1 is of little mathematical importance in the statistical analysis. (Alternatively, either method of statistical analysis could be applied to Uosm and V, but since Posm is constant the results would be identical with those reported in Table II.)

The average values (including all subjects)

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of the mathematically equivalent terms, the intercept a of equation 2, and the slope a of equation 1, are, respectively, 3.16 and 3.13.*

(The possible significance of urea in this problem, and of the non-urea osmotic U/P ratios [Table 1], are discussed in the section "Medullary Blood Flow".)

Emptying and Dead Space Errors. A high positive correlation between V and C_{OBM} , as shown in Figure 2, would be expected if, for any reason such as error related to increased drainage from the renal pelvis or more complete emptying of the bladder, progressively increasing volumes of urine of essentially constant composition and osmotic concentration were collected in successive samples. This possibility is negated, however, by the observed changes in the composition of the urine: (1) the endogenous creatinine U/P ratio decreases, see Figure 1; (2) the urine sodium concentration decreases (U_{Na}), see Table 1;

and (3) urine sodium osmotic fraction $\left(\frac{U_{\text{Na}}i}{U_{\text{OSM}}}\right)$ in-

creases (Fig. 3), and, in consequence of (3), the potassium and urea osmotic fractions decrease, as between the periods of minimal and maximal urine flow. (These relations do not hold true in the last two periods in one subject [M. C.] and the last five periods in another subject [H. V.], which may involve emptying errors or a decrease in filtration rate reflexly induced by suprapubic pressure.)

Filtered Sodium Load. To what extent increased natriuresis is attributable to increased filtration rate in the supine position cannot be ascertained from our data. Urine samples collected at the low flows involved in this study are inevitably subject to substantial emptying errors and, where the urine flow is increasing, also to dead-space errors. Emptying errors (but not dead-space errors) can, as a first approximation, be eliminated by averaging the values of V and (endogenous) creatinine U/P ratio in each pair of successive urine collection periods; a "smoothed" creatinine clearance calculated from these averaged values reduces the mathematical weight of incomplete emptying in one period when followed by complete emptying in the next. As shown in Figure 3, the smoothed creatinine clearance increases in some subjects and decreases in others, and in any case it may or may not accurately reflect changes in the filtration rate. However, it is immaterial to this study whether the natriuresis is of glomerular or tubular origin—our immediate emphasis is on the primacy of

the increase in sodium excretion in the supine position, a phenomenon which has been well documented by others [41], although not in the hydropenic state and with short period urine specimens collected by catheter, as recorded here.

Diurnal Cycle. The circumstance that our observations have been made in the morning hours, when sodium excretion is generally increased in relation to the diurnal cycle, raises the question whether or not the diuresis reported here has its origin solely in this cycle. The extensive literature on diurnal variation in the excretion of electrolytes and water need not be cited here because all these studies have been limited to voided specimens and to urine collection periods extending from one to several hours, with little reference to the effects of changes in posture. Thomas [46], however, has recently shown that in moderately hydrated subjects who voided voluntarily every thirty to sixty minutes, increased sodium excretion was induced by the change from the standing to the recumbent position at all times of day, although generally superimposed on the typical diurnal variation in electrolyte excretion. No short period observations are available on subjects who remain recumbent in the morning hours, and consequently we have made a study, using the same technical approach as is described here, in ten hydropenic subjects who, although awake, maintained the supine position without interruption in the morning hours. These data will be reported elsewhere, and it will suffice for our present purposes to state that the postural diuresis described here depends primarily on the change in posture and contains a negligible contribution from the diurnal cycle.

Collecting Ducts. Although postural diuresis cannot be explained by emptying errors involving the bladder and renal pelvis, one may ask, in view of the constant osmotic pressure of the urine, whether it may only represent an increased discharge of urine from the collecting ducts wherein the urine is concentrated. With certain qualifications, this interpretation could at least in part explain the decrease in creatinine U/P ratio, the increase in urea excretion and the increase in $T_{\rm HaO}^{\rm c}$.

In considering this question, we return to the point that the primary event in postural diuresis is an increased excretion of sodium. If the diuresis arises solely in the collecting ducts it must be in consequence of decreased sodium reabsorption in these ducts. Hilger, Klümper and Ullrich [15] interpreted the data obtained by catheterization of the ducts in the hamster as indicating that some sodium is directly absorbed (presumably as sodium chloride) in the ducts, but in later evaluations Ullrich [48,49] implies that the decrease in sodium concentration between the outer and inner medullary zone can largely be accounted for by Na⁺:H⁺-ion exchange or, subordinately, the capture of NH₃ as NH₄⁺ after urine acidification [50]. Jaenike and Berliner [18] leave the question

^{*} We are unable at this time to reconcile our observations on postural diuresis in man with the increase in urine osmotic pressure observed in the kidney of the dog when the filtration rate is moderately reduced by partial constriction of the renal artery, as reported by Levinsky, Davidson and Berliner [23].

of sodium chloride reabsorption by the ducts in the dog an open one. Hence there is at present no definite evidence of sodium chloride reabsorption by the ducts. However, solely for argument we may assume that such reabsorption does occur, and that it may be reduced in the supine position. All the available data indicate that the urine osmotic pressure increases progressively down the entire length of the ducts to reach its maximal value at the tip of the papilla [12,15,56]. It is semantically futile to argue that the diuresis could arise at the extreme distal end of the ducts where the urine is maximally concentrated and after all changes in urea and potassium concentration have been completed. Rather the proposition must envisage decreased sodium and water absorption throughout some substantial portion of the ducts, in which case the volume of relatively dilute urine moving down the ducts will be increased; the intrinsic concentrating operation remaining constant, the net effect of this diuresis will be to dilute the medullary interstitium of the distal papilla and to lower the maximal concentration of the urine. If such sodium as is excreted at the peak of diuresis had been previously contributing to the countercurrent system [15,47], its loss in the urine would reduce the osmotic pressure of the final urine to an even greater extent. Hence decreased sodium chloride reabsorption in the collecting ducts would not, it seems, explain the fact of the constant urine osmotic pressure.

Thomas [45], using thirty to sixty minute urine collection periods, has shown that, relative to standing, the excretion of NH4+ and titratable acidity is decreased and the excretion of HCO₈ is increased in the recumbent position, revealing a decrease in the Na+: H+-ion exchange mechanism in recumbency (which he attributes partly to decreased aldosterone secretion). Decreased acidification of the urine amounts in the net to an increase in the excretion of NaHCO3 and substitution of Na2HPO4 for NaH2PO4, both of which would operate to increase COSM, while substitution of NaA for NH4A would have no effect on COSM. Combining the maximal increase in the excretion of HCO₃ (40 µEq. per minute), as reported by Thomas [45], with an estimated increase in sodium excretion derived from conversion of NaH2PO4 to Na₂HPO₄ (20 μEq. per minute [25]) yields a maximal increase of 60 µOsm. per minute, or 0.20 ml. per minute in osmotic clearance. This figure is so far short of our observed average increase of 1.28 (or extreme increase of 1.97) ml. per minute that postural natriuresis can scarcely be explained by a decrease in Na+: H+ion exchange activity.

Apparently only a small Na⁺:K⁺-ion exchange operates in the collecting ducts [14,15,18,48,49,53]. The fact that potassium excretion is increased in postural diuresis suggests that either potassium secretion is immediately stimulated by the supine position, an unlikely supposition, or that sodium absorption is reduced at some point proximal to the distal con-

voluted tubule, the locus of the major $Na^+:K^+$ -ion exchange mechanism [18]. But the substitution of potassium for sodium would not decrease the creatinine U/P ratio or increase the excretion of urea or the net value of C_{OSM} . We are consequently led to conclude that the natriuresis reported here is a result of decreased sodium reabsorption at some point proximal to the collecting ducts, and other than in the concentrating mechanism in Henle's loop, since this natriuresis is not accompanied by a decrease in the intrinsic concentrating operation.

COMMENTS

It is tempting to equate a constant urine osmotic pressure, as observed here during postural diuresis, with a constant, effective osmotic concentration in the medullary interstitium; also, since the hyperosmotic state in the medulla is, in the first instance, established by sodium absorption in the loop of Henle, to inquire what bearing our results may have on this process.

The supposition that the elaboration of osmotically concentrated urine involves the active transport of water in any segment of the nephron has been effectively negated by the application of Kuhn's countercurrent multiplication theory, as developed by Hargitay and Kuhn [13] to the renal medulla [56]. Although the literature on this mechanism has been recently reviewed [2,12,42], our immediate discussion requires reference to certain details.

On several lines of evidence, it is accepted that sodium (presumably with chloride) is actively absorbed from the tubular urine in the loop of Henle, to be deposited, externally to the loop, in the medullary interstitium. The operation of the elongated loop is such that the interstitial sodium concentration, and hence the interstitial osmotic pressure, increases progressively from the corticomedullary junction to the tip of the papilla. Almost unequivocal evidence indicates that in the presence of the antidiuretic hormone (ADH) both the distal convoluted tubule and the collecting duct are essentially freely permeable to water; the urine emerging from the distal convoluted tubule is therefore isosmotic with the (systemic) blood in the cortical peritubular capillaries; but as this urine passes down the collecting duct water is passively (osmotically) abstracted into the hyperosmotic medullary interstitium, with the consequence that the urine emerging from the papilla is isosmotic with the latter and correspondingly hyperosmotic to the systemic blood.

(Some important qualifications on this point are given in the section "Osmotic Equilibration".)

The mathematical treatment of the countercurrent multiplication system, as developed by Hargitay and Kuhn [13], affords no immediate aid in the exploration of this problem because certain parameters basic to a detailed quantitative treatment of the kidney are unknown and cannot be replaced by speculation. The physiologic problem must therefore be approached empirically.

A constant interstitial osmotic concentration requires that so long as the medullary blood flow is constant (see section on "Medullary Blood Flow"), the respective rates at which osmotically active solutes, on the one hand, and solute-free water, on the other, are added to the interstitium must remain in some fixed ratio:

(3)
$$\frac{\Delta \text{ solute}}{\Delta \text{ water}} = k$$

Ignoring urea (which enters the interstitium from the concentrated urine in the collecting duct) for reasons which are discussed in the section, "Role of Urea," sodium is the most important solute, the net concentration of which is altered in the interstitium and transferred into the interstitium by active absorption from the tubular urine in the loop. This sodium represents, in effect, solvent-free solute added to that which is constantly circulating through the medulla via the vasa recta. This added sodium is removed from the medulla by the blood in the ascending vasa recta. For brevity, we may designate the moiety of sodium absorbed from the loop (expressed as microequivalents per minute) as T_{Na}^{loop}. As a working assumption (see section, "Descending Thin Segment") we will treat the descending thin limb of the loop as permeable to water and sodium chloride, in which case fluid leaving (or entering) the descending limb at any level will be isosmotic with the interstitium at that level. Under this assumption, the only net solute-free water entering the medulla is that which is abstracted from the urine in the collecting ducts. This solute-free water is identical with Tetao, the water (expressed in milliliters per minute) which must be added to the bladder urine in order to dilute the latter back to the isosmotic state [57] at which it enters the collecting ducts:

(4)
$$T_{\text{H}_{2}\text{O}}^{\circ} = C_{\text{OSM}} - V$$

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Writing Δ solute = iT_{Na}^{loop} and Δ water = $T_{H_2O}^e$, equation 3 becomes:

(5)
$$\frac{iT_{\text{Na}}^{\text{loop}}}{T_{\text{H2O}}^{\text{c}}} = k = I_{\text{OSM}} - P_{\text{OSM}}$$

where T_{Na}^{loop} and $T_{H_4O}^{\circ}$ by definition represent the only net additions of sodium and water to the interstitium and i is the osmotic coefficient of sodium chloride in the interstitium. This ratio has the virtual dimensions of an increase in interstitial osmotic pressure (I_{OSM}) over and above that of the blood (P_{OSM}) entering the medulla.

It may be repeated that T^e_{H₂O} increases by 1 ml. per minute or more in some of our subjects (C. C., A. S., E. B., M. K., A. J.), attaining peak values in excess of 2 ml. per minute; an increment in T^e_{H₂O} of 1 ml. per minute represents some 20 per cent of the average maximal value of T^e_{H₂O} (5 ml. per 100 ml. of glomerular filtrate) observed during copious osmotic diuresis [6,57] and it would be anticipated that changes in T^e_{H₂O} of this magnitude would effect significant dilution of the medullary interstitium if sodium absorption by the loop were constant.

In short, the maintenance of a constant urine osmotic pressure in the face of an increasing (or decreasing) value of T_{H2O} implies that T_{Na}^{loop} increases (or decreases) in proportion to T_{H₂O}. The simplest explanation of this proportionality would seem to lie in the possibility that, within the range of variation of Teto encompassed by the present observations, the transport of sodium by the loop is critically limited by the concentration of sodium in the interstitium, or by a concentration gradient between the tubular urine and the interstitium, so that as increasing absorption of water from the collecting ducts tends to dilute the interstitial sodium, sodium transport increases sufficiently to offset this dilution.

It may be inferred from all studies in this area that the concentrating operation in the oliguric kidney of the mammal has some upper limitation characteristic of the species—in man, for example, as represented by an osmotic U/P ratio of about 4—and characteristic also of the individual person, although subject of course to the degree and duration of dehydration and to other physiologic variables. Correction for diffusion of urea into the medulla (as discussed in the section "Role of Urea") or for diffusion of water, etc., across the ureters and bladder

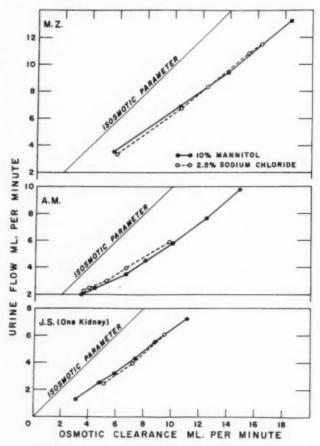


Fig. 5. Comparison of renal concentrating power in three subjects during mannitol and hypertonic sodium chloride diuresis. (All three subjects were hypertensive.) This figure is to be compared with Figure 8 of Gottschalk and Mylle [12] which shows that the rat concentrates substantially better during saline than mannitol diuresis.

(see section "Transureteral Diffusion") can at most qualify the magnitude of this maximal osmotic gradient.

In the light of many recent studies it must be accepted a priori that a limiting osmotic gradient involves two-way flux of both sodium and water (and probably other substances) across that portion of the loop which is involved in active sodium transport, as well as across the epithelium of the collecting ducts; the limiting gradient probably also involves a dynamic balance (or steady state) among such variables as urine flow in the loop, blood flow in the vasa recta, differential molecular diffusion in the interstitium, urine flow in the collecting ducts, etc.

Because of these unquantified variables, no choice is presently possible between a limitation imposed by a sodium concentration gradient and one imposed by the interstitial sodium concentration *per se*. Some support for a gradient limitation can be derived from observations on active

sodium transport in the proximal tubule, as noted in section "Osmotic Ceiling" even though against a gradient limitation is the similarity of the concentrating operation in man during mannitol and hypertonic saline diuresis. During mannitol diuresis the sodium concentration in the urine entering the ascending limb of Henle's loop must be reduced in a manner roughly parallel to that observed in the proximal tubule during mannitol diuresis [51,52]; whereas this concentration is, if anything, increased during hypertonic saline diuresis. And yet, as shown in Figure 5, the net concentrating operation is almost identical in the two circumstances. It may be that in man, however, mannitol diuresis sufficient in magnitude to produce urine flows in excess of 25 ml. per minute is required to reduce the sodium concentration in the loop significantly.*

The idea that some limitation is imposed on sodium transport in Henle's loop finds support, at least in analogy, in the relatively constant sodium concentration characteristic of the secretion of the nasal glands (or "salt glands") of the marine birds [33] and reptiles. (The only other cation in this secretion is potassium, which is present in comparatively small amounts.) Here, however, the higher concentration pertains to the fluid secreted into the lumen of the gland, i.e., on the apical surface of the epithelial cell; in the cormorant the sodium concentration in the secretion (in mEq. per L.) ranges from 500 to 600 [36], in the herring gull from 700 to 800 [9], in the Humboldt penguin from 726 to 840 [37], in the albatross from 726 to 840 [10], in the brown pelican from 637 to 764 [34], in the diamond back terrapin from 616 to 784, and in the loggerhead turtle from 732 to 878 [35]. Data on the sodium

* With respect to the relative effects of mannitol and hypertonic saline diuresis (Figure 5), our observations in man do not agree with those reported in the rat by Gottschalk and Mylle [12] (see their Figure 8). In this species concentrating power is substantially lower during mannitol diuresis than during hypertonic saline diuresis. This discrepancy may be related to a species difference, in that the rat may have a lower filtration rate and a less luxus filtered load of sodium, relative to the reabsorptive activity of the proximal tubule and loop of Henle, than does man, so that during increasing mannitol diuresis the sodium concentration in the urine is more rapidly reduced to values limiting absorption in the loop. The possibility that during extreme mannitol diuresis, active sodium absorption by the loop may be curtailed by an increased concentration gradient may in part explain the decrease in sodium and chloride concentrations in papillary slices of the kidney of the dog, as reported by Malvin et al. [24].

concentration in the plasma of the marine birds and reptiles are not available, but the freezing point depression of the blood in marine turtles ranges from 0.66 to 0.76°c., so that the secretion is osmotically at least three times as concentrated as the blood. (The osmotic U/P ratio in fasting marine turtles appears to be a little less than 1 [40].) Acetazolamide reduces the rate of secretion of fluid in the herring gull without reducing the sodium concentration [27].

Accepting the inference that, at low rates of influx of solute-free water (Te_{H2O}) into the medullary interstitium, sodium absorption by the loop is concentration-limited in one way or another, it must be accepted in principle that this limitation cannot keep pace indefinitely with an ever increasing inflow of diluent. And more as a speculation than logical deduction, we conceive that when T_{H2O} is sufficiently large, the concentration limitation gives way to a maximal rate limitation (Tm_{Na}), and that it is this maximal rate limitation which explains the fact that during marked osmotic diuresis, when the inflow of isosmotic urine into the collecting ducts is large and the available water is proportionally increased, the quantity of water abstracted from the urine in the ducts attains an approximately maximal value (Tm^c_{H₂O}). This was first demonstrated by Zak, Brun and Smith [39,57] and confirmed in man by several investigators [1,4,6, 44], in the dog by Page and Reem [28] and more recently by Giebisch and Lozano [11] and Epstein and his co-workers [8], in the rat by Koike and Kellogg [20] and Corcoran, del Greco and Masson [7].

SUMMARY

When previously ambulatory, hydropenic subjects (with or without vasopressin) assume the supine position, there ensues a transient osmotic diuresis attributable primarily to increased excretion of sodium. The excretion of potassium and urea are also usually increased, but only secondarily, it appears, to the increased natriuresis.

This osmotic diuresis is characterized by a constant urine osmotic concentration (with or without subtraction of urea) over a small but physiologically significant range of urine flow.

It is postulated that as long as the rate of influx of solute-free water into the medullary interstitium (calculated as T^o_{H2O}) is less than a critical value (ca. 2 ml. per minute), the transport of sodium by the loop of Henle into

the medullary interstitium is limited either by the concentration of sodium in the interstitium or by the concentration gradient between the urine in Henle's loop and the interstitium, with the consequence that the interstitial osmotic pressure, and hence the urine osmotic pressure, remains constant in the face of increasing urine flow and increasing influx of solute-free water $(T_{H_2O}^e)$ into the medulla.

It is suggested that when the rate of influx of solute-free water $(T^{e}_{H_2O})$ is critically increased, as during marked osmotic diuresis, the 'concentration' limitation in sodium transport by the loop gives way to a maximal rate limitation, and the rate of removal of solute-free water from the urine attains the approximal constant and maximal value $(Tm^{e}_{H_2O})$ previously described during mannitol diuresis.

APPENDIX

Certain difficulties pertaining to the quantitative treatment of the medullary concentrating system in man must be appended to this discussion, if for no other reason than to emphasize the limitations they impose on our present interpretation.

Osmotic Equilibration. Although micropuncture studies relate to fluid collected from closely adjacent loops, vasa recta and collecting ducts in the same animals, perfect agreement between these papillary elements is not invariable, as is shown by Figure 10 of Gottschalk and Mylle's paper [12]. The assumption that the urine in all collecting ducts is perfectly equilibrated with the interstitium at any level of the medullary substance, or even at the tip of the papilla, is possibly unwarranted because it ignores the known anatomical diversity of the cortical and juxtamedullary nephrons, variable relations between thin segments and collecting ducts with respect to length, number, etc. Hence we use the terms "medullary interstitium" and "interstitial osmotic pressure" in a frankly ambiguous way, to designate some undetermined integral of the interstitial fluid of the inner medulla.

It is improbable that the velocity of urine flow through the collecting duct militates against osmotic equilibration between urine and interstitium at such low flows as are involved in this study. In Table 6 of their paper Gottschalk and Mylle [12] have shown in the hamster, kangaroo rat and the rodent, Psammomys obesus, that the urine near the tip of the loop and that in the collecting duct are generally very close to osmotic equilibration, even during substantial osmotic diuresis. At urine flows of 1 ml. per minute or less in man it seems safe to assume that the osmotic equilibration of water between the collecting duct urine and the interstitium is complete, subject to the anatomic diversity already mentioned.

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Medullary Blood Flow. In the foregoing discussion we neglect the possible effects of posture on medullary blood flow. Since the sodium (and water) added to the interstitium are carried away by the blood in the ascending vasa recta, increased medullary blood flow, at least above some critical value, will diminish the effectiveness of the concentrating mechanism. Change from the ambulatory state to the supine position would, if anything, tend to increase total renal blood flow, but to what extent the vasa recta would participate in this increase, or what quantitative effect any increase would have on the concentrating mechanism, is undetermined. Qualitatively, however, our results are contrary to what would be expected (decrease in Uosm) if the supine position were accompanied by substantial medullary hyperemia.

Role of Urea. A major difficulty in relating urine osmotic pressure to sodium absorption in the loop of Henle is presented by urea. Klümper, Ullrich and Hilger [19] and Levinsky, Davidson and Berliner [23] have shown that the permeability of the collecting duct to urea is such that this compound diffuses from the collecting duct urine into the medulla, to reach high concentrations in the latter. The actual quantity escaping from the urine need not be large in order to maintain a high concentration in the medullary interstitium because it is trapped therein by the countercurrent diffusion operation of the vasa recta. Klümper et al. [19] using the microcatheter method, reported that in the hamster an average of 35 per cent of the urea entering the collecting ducts is lost by outward diffusion. This fraction is, however, highly variable, as shown both by their data and by the fact that Levinsky and his co-workers [22,23] found that the urea concentration per kilogram of water in the papilla of the dog ranges from 5 to 40 per cent below that of the urine excreted just antecedently. (The urea concentration in whole papillary tissue will be reduced by the urine in the loop of Henle if this urine has a lower concentration than does the collecting duct urine [and lower than the interstitium], and also by intracellular water if urea does not penetrate all cellular elements freely. Tissue analyses must therefore be accepted with some reservation at this time).

As Miles, Paton and de Wardener [26] first pointed out, insofar as the cells at the most distal site of water reabsorption (collecting ducts) are permeable to urea, the "effective" osmotic gradient (for water) will be less than that indicated by the total urine osmotic pressure. This point has been elaborated by Levinsky, Davidson and Berliner [23]. For this reason, urea as a solute is excluded from "solute-free water," as this expression is used herein; although urea may be osmotically inactive itself, a "urea solution" moving from the collecting duct urine into the interstitium will decrease the effective (sodium) osmotic concentration in the latter as much as would urea-free water.

We know nothing about the urea interstitium/urine ratio (I_{UR}/U_{UR}) in man, and speculations on this

point are scarcely justified, particularly under circumstances where the velocity of urine flow and the urine urea concentration are both changing, as in our experiments. However, solely to the end of testing our data for the possible significance of urea we have examined the consequences of the simplest (even if not valid) assumption that the I_{UR}/U_{UR} ratio is 1. Hence $I_{UR} = U_{UR}$, and the non-urea osmotic U/P ratio* defining the true osmotic gradient for water will become:

$$\frac{U_{OSM} - U_{UR}}{P_{OSM} - P_{UR}}$$

Table I gives the non-urea osmotic U/P ratio for all recumbent periods; as would be expected, this value is substantially less than the total osmotic U/P ratio. The non-urea osmotic clearance takes the form:

(7)
$$C_{OSM-UR} = \frac{U_{OSM} - U_{UR}}{P_{OSM} - P_{UR}} V$$

Statistical analysis of the non-urea osmotic U/P ratio with $\frac{1}{V}$ (equation 2) for the eleven subjects for whom urea data are available shows that the linear correlation of C_{OSM-UR} with V is better than that of total C_{OSM} with V (also calculated by equation 2) in three subjects, remains the same in six, and becomes worse in two. It can only be said that the same conclusion regarding the constancy of the urine osmotic pressure during postural diuresis is reached, whether or not the urine urea is wholly excluded (U_{OSM-UR}) or wholly included (U_{OSM}) . Thus there is no reason to assign any special significance to urea in interpreting our present data.

Descending Thin Segment. A major difficulty in our knowledge of the medullary system lies in the fact that the permeability characteristics of the descending limb of the thin segment of the loop of Henle are unknown. Active sodium absorption may be attributed with confidence to the proximal convoluted tubule (on this point a substantial literature is now available, including micropuncture studies), probably to the thin ascending limb and, more confidently, to the pars recta of the distal tubule, as well as to the entire distal convoluted tubule (see Jaenike and Berliner [18]). Sodium is reabsorbed by an exchange mechanism for K⁺ and H⁺ in the distal convoluted tubule and to a lesser extent in the collecting duct [5,18,53].

The ascending limb of the thin segment and the pars recta remain relatively impermeable to water even in the presence of the antidiuretic hormone (ADH), while the distal convoluted tubule and the collecting

 * $U_{\rm OSM}$ and $P_{\rm OSM}$ are again molal concentrations, and $U_{\rm UR}$ and $P_{\rm UR}$ are molar concentrations; the immediate error involved in using these incommensurate terms is negligible. This calculation also assumes that no solute other than urea escapes by diffusion out of the collecting duct.

duct are permeable to water only in the presence of this hormone. The foregoing statements are based in part on micropuncture studies [12,54,55] and in part on the recent observations of Jaenike and Berliner [18].

The properties of the descending limb of the thin segment of the loop, however, are experimentally undefined and remain open to two interpretations. (1) As a working assumption, Wirz [55] and Gottschalk and Mylle [12] treated this segment as permeable to both sodium and water, limiting net active sodium absorption to the (water-impermeable) ascending limb. However, Dr. Gottschalk has pointed out to us that the available data would conform with the alternative interpretation, that (2) active sodium absorption may in principle also be attributed to the descending limb (as conceived by Berliner and his colleagues [2]), if it is posited that this limb (at least in the presence of ADH) is permeable to water; this condition supplies the simplest explanation of the fact that in hydropenia the tubular urine at the tip of the loop is isosmotic with the interstitium and collecting duct urine [12]. This interpretation is attractive because it ascribes to the descending thin limb the same functional properties, so far as sodium and water are concerned, as are now accepted for the proximal convoluted tubule, except for the circumstance that it is immersed in the hypertonic medullary interstitium; thus active sodium absorption would be a property of all parts of the nephron, from the beginning of the proximal tubule to the end of the collecting duct. This interpretation has the disadvantage, however, that it would reduce the quantity of urine delivered to the more distal parts of the nephron and thus reduce the quantity of water available for excretion as osmotically free water during water diuresis.

Alternatively, it may be that the descending thin limb, although permeable to water in the presence of ADH, is relatively impermeable to sodium and urea; the abstraction of water into the hyperosmotic interstitium would suffice to bring the urine to an equally hyperosmotic state at the tip of the loop. Even though no choice between these two interpretations can be made on the available evidence, in the foregoing discussion we have accepted, with Wirz and Gottschalk and Mylle, the working hypothesis that the descending limb is permeable to both sodium and water.

If the contrary hypothesis is preferred, namely that the descending thin limb is freely permeable only to water (without active sodium absorption), then the water entering the hyperosmotic interstitium will contribute to the dilution of the interstitial sodium, as does that abstracted from the collecting ducts. Indicating this solute-free water as $T_{\rm H_2O}^{\rm loop}$ (where the superfix *loop* indicates any part of Henle's loop), the denominator of the left-hand term in equation 5 must read $T_{\rm H_2O}^{\rm e} + T_{\rm H_2O}^{\rm loop}$; as long as the urine flow into the descending limb remains constant, the immediate effect of this additional water will be to increase the

presumptive value of $T_{\rm Na}^{\rm loop}$ at any specified values of $U_{\rm OSM}.$

Transureteral Diffusion. Levinsky and Berliner [21] have shown that when the dog's ureter is perfused in vivo from pelvis to bladder at low rates of flow, water, urea and sodium chloride diffuse across the ureter (or bladder) along their respective concentration gradients, the extent of diffusion increasing as the perfusion rate decreases. More recently, Rapaport, Nicholson and Yendt [29] have demonstrated significant diffusion of electrolytes across the intact or isolated bladder of the dog in periods ranging from one-half to six hours. The possibility of transureteral and transvesicle diffusion presents a major difficulty in the study of very concentrated (and also very dilute) urine in man, a difficulty which can be avoided only by unilateral catheterization of the renal pelvis. Despite its technical difficulties, attempts are now being made to study this problem in man.

In advance of definitive studies, we may assume that water will diffuse more rapidly than urea or sodium, and that the chief effect of diffusion will be to dilute a concentrated urine, the extent of dilution varying inversely with urine flow. One would expect that urine formed at the lowest flow (i.e., early in the supine position) would suffer greater dilution than that collected at a higher flow, but Figure 1 and the statistical analysis in Table II reveal no consistent drift in UOSM. Moreover, if diffusion were important in man one would expect Uosm to increase consistently as between the ambulatory specimen (A in Table 1) and the first period of recumbency (S1 in Table 1), since these represent decreasing periods of retention in the bladder. But the changes in Uosm are small and randomly distributed. We can only proceed at present on the premise that diffusion in our fifteen minute collection periods is not of such a magnitude as to jeopardize the significance of our observations.

Osmotic "Ceiling." As noted in the text, the Hargitay-Kuhn [13] mathematical treatment of the countercurrent multiplication system does not contain the essential terms which would set an upper limit to concentration in relation to the variables in the system, and the properties of the mammalian kidney must be explored empirically.

Supplementing what has been said in the text on a possible concentrating-gradient limitation in sodium transport in the loop, it may be noted that sodium absorption by the proximal tubule in the dog appears to be limited by a concentration gradient of some 75 mEq. per L. [51], while in Necturus this gradient has been more directly and accurately established at 35 mEq. per L., at which point retrograde flux into the tubular urine equals active transport outward, and net sodium (and water) absorption ceases [52]. During mannitol diuresis a sodium concentration gradient of fairly uniform magnitude may conceivably be maintained throughout most of the length of the proximal tubule. However, the situation is different

in the ascending limb of Henle's loop. The urine entering this limb at the tip of the loop is isosmotic with the interstitium, and the sodium concentration in this urine is probably equal to that in the interstitium, and may be much greater if the descending limb is not freely permeable to urea; whereas the absorption of sodium by the ascending limb has reduced the osmotic concentration in the urine reaching the distal convoluted tubule to a level (100 to 200 mOsm.) well below that of the plasma, and here the sodium concentration must be less than that of the plasma. In the interstitium, on the other hand, the sodium concentration apparently increases progressively from the outer medulla to the tip of the papilla. It would seem more fortuitous than probable that these two concentration terms, changing in opposite directions, should change in so parallel a manner as to maintain a constant sodium gradient between urine and interstitium down the length of the loop-unless, indeed, outward active transport and inward flux are so intrinsically inter-related as to establish this very gradient. Answers to these questions must await knowledge of the sodium and perhaps urea concentrations in both the descending and ascending limbs of the loop.

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Hemodynamics of Idiopathic Orthostatic Hypotension*

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TDIOPATHIC orthostatic hypotension is a rather rare entity, and in only a few communications are hemodynamic studies, including cardiac output, reported [5,37]. It is an acquired disease, and represents failure of the normal mechanisms governing arterial blood pressure, and in some instances cardiac output. Secondary orthostatic hypotension may appear as a result of various diseases involving the nervous system including diabetes mellitus, syringomyelia, multiple sclerosis, traumatic cord lesions, as well as those forms induced by surgical sympathectomy. Hemodynamic studies of these patients also are limited [4,5,37,46].

It is the purpose of the authors to describe the syndrome of idiopathic postural hypotension, using the case histories of two subjects as illustrative examples, and to report the results of our hemodynamic studies. Evidence will be presented to support the concept that hemodynamic maladjustment may be present in recumbency as well as in the erect or tilted position. A review of the pertinent literature is included in the discussion.

METHODS

The tilt table test was performed with the use of a fluoroscopic table capable of tilting from the horizontal to a vertical position within ten seconds. The patients' weight was supported in the tilted position by means of a footboard. When control pulse and blood pressure became stable in the supine position, the patient was tilted feet down to various degrees from the horizontal. The results of changes in pulse and blood pressure were plotted against time and degree of tilt. (Fig. 1.)

Cardiac output was determined by a modification of the Hamilton dye dilutional technic [47] using a Colson cuvette densitometer [48] as the monitoring device of arterial dye concentration. In using this

method it is essential that the dye be delivered into the circulation in an accurately quantified amount, and (theoretically) instantaneously. In this laboratory we have employed specially constructed calibrated glass cartridges fitted with three way stopcocks on either end. The cartridges are so constructed that the contained dye may be cleared from the lumen by flushing 10 to 15 ml. of saline solution from a syringe directly through them into a peripheral vein. This insures rapid and complete injection of a known quantity of dye. Approximately 5 mg. of a tricarbocyanine dye (Cardio-Green®) [49] is injected. A continuous record of dye concentration in arterial blood is obtained by constant withdrawal of blood, via a Riley needle placed in the radial artery, through the cuvetted densitometer by means of a motor driven syringe. The output of the densitometer is fed into an appropriate galvanometer and the curve is recorded on photographic paper.

Over 200 cardiac outputs have been performed in this laboratory in the past eighteen months using these technics. Since one of our major goals has been to study cardiovascular emergencies at the bedside, all cardiac outputs are estimated, by design, under random conditions, without regard to the basal state of the patient. In those without intrinsic cardiovascular disease or thyroid dysfunction, the cardiac index of all patients studied thus far has been within the limits of 2.5 to 4.5 L./min./M². Duplicate determinations check within plus or minus 7 per cent.

Intra-arterial blood pressures were recorded in experiments in which the cardiac output was determined. An inductive electromanometer with carrier amplifier and syringe pressure head was utilized and mean pressures were obtained by electrical integration.

Peripheral vascular resistance was calculated from the following formula:

P.V.R. =
$$\frac{P(m) \times 1332}{\text{C.O. cm.}^3/\text{second}}$$
 dynes second cm⁻⁵

where P(m) indicates mean arterial pressure, and C.O. indicates cardiac output in cubic centimeters

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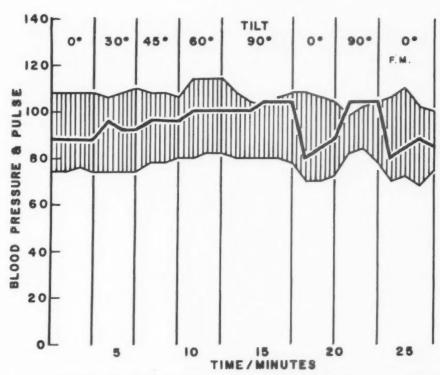


Fig. 1. Graphic representation of the response of pulse and blood pressure to tilting in a normal person. Supine (zero degrees); standing (90 degrees).

per second. It is recognized that this formula yields only an approximation of peripheral vascular resistance [5], and the numerical values given for this parameter are intended only to relate the changes which occur in the ratio of blood pressure to cardiac output in the same person under different conditions.

CASE REPORTS

CASE I. E. K., a forty-one year old male engineer, was admitted to the Buffalo General Hospital on December 11, 1958, complaining of profound weakness on exertion. His symptoms began six months prior to admission when he noted weakness and lightheadedness during periods of strenuous activity. These sensations became progressively more frequent and later were associated with dim vision, loss of coordination, and collapse. The attacks had always occurred when the patient was standing. He was able to regain his strength and equilibrium within two or three minutes by assuming a posture with both hands and knees on the floor. On two occasions the patient lost consciousness for brief periods during the attacks. He denied ever having chest pain, dyspnea or edema and had suffered no recent or remote serious illness. No family history of diabetes, epilepsy or similar diseases could be obtained.

On physical examination the patient was a slightly obese, healthy appearing man. The blood pressure in the supine position was 110/70 mm. Hg. A complete physical and neurologic examination failed to reveal any abnormalities except for a difference in the degree

of perspiration on the left as compared to the right side of the body. When the patient assumed the erect posture the blood pressure was often unobtainable. Ophthalmodynamometry revealed that the diastolic pressure in the retinal arteries was equal bilaterally, and comparable to the prevailing diastolic pressure as measured in the arm. A routine urinalysis and hemogram were within normal limits, as was an oral glucose tolerance test. The serum sodium was 140, potassium 5.9, calcium 5.7, and phosphates 2.3 mEq./L. The blood urea nitrogen was 23 mg. per cent. The spinal fluid had a normal pressure and contained one polymorphonuclear leukocyte and three lymphocytes per cubic millimeter. Spinal fluid protein was 31 mg per cent, the Wassermann test had negative results and the colloidal gold test 0000000000. The twenty-four hour urinary 17-ketosteroid excretion was 11.1 mg. An electroencephalogram was performed, after which the patient stood, collapsed, and had a grand mal seizure with urinary incontinence and then promptly regained consciousness. The electroencephalogram was reported as within normal limits. Roentgenograms of the skull and chest revealed no abnormalities and the results of a number of electrocardiograms were normal.

Various therapeutic measures and procedures were utilized in an attempt to alleviate the patient's symptoms. He was given a high sodium diet with supplementary sodium chloride tablets, and eight inch blocks were placed under the head of his bed. In an attempt to augment venous return, elastic stockings

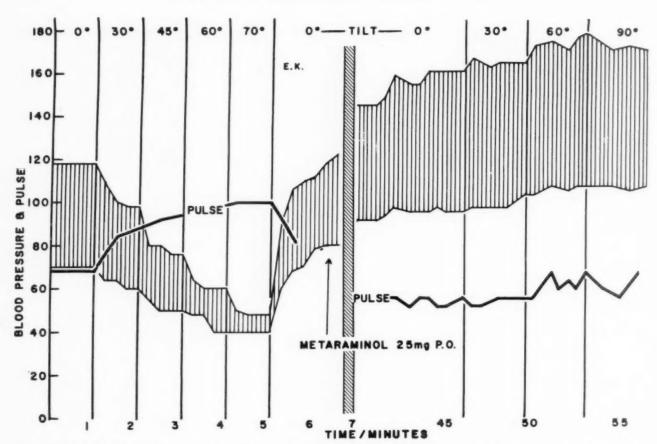


Fig. 2. Tilt table study of one patient (E. K.) with idiopathic orthostatic hypotension. The right side of the figure represents the response to metaraminol therapy.

and a snugly fitted abdominal binder were utilized. Ephedrine sulfate was prescribed four times daily, 9-alpha fluorohydrocortisone [30] also was administered. These agents either alone or in combination had no detectable effect on either his symptoms or blood pressure. The effect of metaraminol on his symptoms, blood pressure and hemodynamics will be described subsequently. The patient later elected to be followed up in a Veteran's Administration Hospital, where a counter pressure garment [37] was fitted, resulting in a limited degree of improvement.

Case II. B. K. M., a sixty-three year old male automobile salesman, was admitted to the Buffalo General Hospital on June 12, 1959. He complained of weakness while in the standing position, of five years' duration. This was gradually progressive and was often associated with blurring of vision and giddiness, occasionally followed by syncope. While standing he had the sensation that "not enough blood was going to the brain." In the course of his work, since he was frequently required to stand in conversing with his customers, his disability had become a source of embarrassment. He had learned that he could usually avert syncope by tensing the muscles of his arms and legs. If this was unsuccessful, he obtained relief by bending over as if to tie his shoes. His symp-

toms were aggravated by exertion, and were worse upon arising than later in the day.

The patient was a tall, slender, alert and intelligent man whose blood pressure in the supine position was 110/60, sitting 70/50, and standing 50/0 mm. Hg. There were no general physical or neurologic abnormalities. Perspiration was normal. Urinalysis, hemogram, glucose tolerance curve, serum electrolytes and cholesterol were within the normal range. The blood urea nitrogen was 20 and 26 mg per cent on two occasions. Excretion of phenolsulfonphthalein was 23 per cent in fifteen minutes, and an additional 29 per cent in two hours. A roentgenogram of the chest, electrocardiogram and electroencephalogram revealed no abnormalities.

Treatment consisted of a high sodium intake, elastic stockings, head blocks and ephedrine sulfate. Initially, although there were no objective signs of improvement, his symptoms were somewhat alleviated. The patient resides out of town, but further study of his condition is anticipated.

INVESTIGATIONS

The normal person maintains arterial blood pressure within a fairly narrow range, regardless of body position. In the tilted position there is a

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tendency for a slight rise in diastolic pressure and a slight fall in systolic pressure, mean arterial pressure being virtually unchanged. Significant acceleration of pulse rate occurs as the position is changed from the horizontal (0 degrees) to the vertical (90 degrees). Figure 1 is a graphic representation of the changes which occur in blood pressure and pulse rate in a normal person subjected to the positional alterations indicated.

Study of alteration of cardiac output by dye dilutional methods in our laboratory in response to tilting yielded data which are in general accord with the results appearing in the literature. In normal subjects some fall in cardiac output is consistently observed during tilt, but the maximum decline has been found to be in the range of 25 per cent below the supine values at a

tilt of 60 degrees.

Subject E. K. (Case 1), the first patient presented herein, demonstrated a remarkable degree of orthostatic hypotension. It should be emphasized that this patient, like others reported in the literature [39], had some day to day variation in the severity of his disability. Nevertheless, his orthostatic difficulty could always be easily demonstrated, and consistently led to symptoms while he was standing. In Figure 2 his usual degree of orthostatic change is demonstrated in blood pressure and pulse rate, and also, on the right side of the figure, the parameters show a response to the administration of oral metaraminol. The impressive fall in both systolic and diastolic blood pressure was quickly reversed by simply returning the patient to the horizontal position. Acceleration of the pulse did occur, but it did not appear to be appropriately augmented for the remarkable degree of hypotension which was present at a tilt of 70 degrees. Following the standard tilt table test, the patient was given 25 mg. of metaraminol orally, and shortly after a response was evident; about twenty-five minutes later, the test was repeated. As shown on the right hand side of Figure 2, there was a progressive increase in blood pressure and orthostatic hypotension was no longer present. It is of some interest that during this hypertensive period there was a bradycardia, suggesting the presence of a responsive carotid sinus reflex, aortic reflex or other undefined regulatory mechanism.

Having demonstrated the effectiveness of metaraminol therapy in restoring the standing blood pressure in this subject, we turned our attention to the physiologic implications of this

phenomenon. In order to demonstrate the hemodynamic dysfunction present, a series of experiments were conducted to obtain measurements of cardiac output and stroke volume, cardiac rate, mean blood pressure and calculated peripheral vascular resistance in the supine and tilted position. The results of these studies were not unexpected, for in the supine position all of these parameters were found to be normal, and during a tilt the cardiac output and peripheral vascular resistance both decreased, resulting in an impressive fall in mean blood pressure. The effects of the administration of metaraminol were also as expected, and depended upon the dose administered. It has been shown [33] that in low doses metaraminol increases cardiac output without having a significant effect on peripheral vascular resistance, while in high dosage the major effect is on the peripheral blood vessels, resulting in intense vasoconstriction. During one experiment a large dose of metaraminol resulted in a blood pressure response of 160/95 mm. Hg (mean 117) at 60 degrees, associated with a cardiac output comparable to that at 60 degrees when metaraminol was not given. The calculated peripheral vascular resistance was over twice that of the control (60 degrees) resistance, and the pulse was slower (60 as compared to 78), again demonstrating a cardioinhibitory response to an elevated blood pressure. It was encouraging to find that, with the proper dose of the drug (approximately 12.5 mg. administered orally), the hemodynamic parameters investigated could be adjusted at a 60 degree tilt to match the normal values obtained when the patient was lying supine. Figure 3 illustrates the hemodynamic alterations which occurred in this subject following tilting as contrasted with two sets of control observations in the supine position, and in the columns at the extreme right, the response to metaraminol therapy while the patient was tilted. The studies here reported were made in chronological sequence, but are also representative of a series of experiments.

When he was given metaraminol the patient was capable of functioning as a normal person. No circulatory symptoms were present during the response, and for the first time in a number of months he was able to climb stairs without having the sensation that he was going to faint. The difficulties encountered with the preparation available to us, however, made its use for long term therapy impractical. Small doses, in the range of 12.5 mg., were quite effective, and

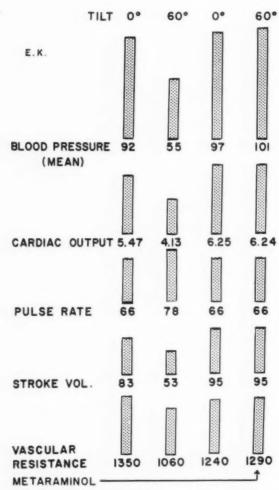


Fig. 3. Hemodynamic parameters obtained from the study of subject E. K. The columns at the extreme right represent values obtained with the patient tilted to 60 degrees, showing the effect of metaraminol therapy.

were without side effects. At this dose level, however, the duration of the response was transient; after administration the peak response occurred in about twenty-five minutes, and after another thirty minutes the effect was dissipated. Larger doses produced a sensation of cerebral congestion, often accompanied by disturbing headache, although the duration of the effect was considerably longer. Figure 4 demonstrates the time-dose relationships of the drug in terms of the standing blood pressure.

The patient's blood pressure response to a sustained forced expiratory effort against a pressure of 40 mm. of mercury (Valsalva maneuver) is shown in Figure 5, and contrasted to the normal response. The interpretation and significance of these pulse tracings will be discussed in a subsequent section.

Patient B. K. M. (Case II), the second patient had learned by experience and necessity to

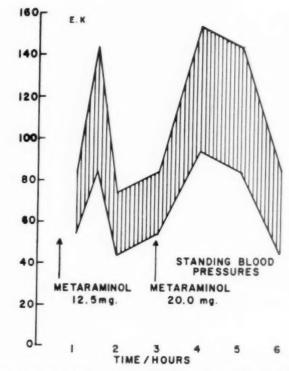


Fig. 4. The effect of the administration of different oral doses of metaraminol on blood pressure of subject E. K. when standing.

augment venous return by active contraction of his skeletal muscles while standing motionless. Considering the results of the studies to be described he was able to compensate for his abnormalities surprisingly well.

The tilt table study of this patient is presented in Figure 6. The hypotensive response to tilting was not quite as dramatic as in Case 1, but was nevertheless impressive. When passively tilted to 60 degrees the patient was on the verge of syncope. His response to 5 mg. of metaraminol given intramuscularly was so intense that his blood pressure rose to 210/104 mm. Hg, regardless of body position.

The hemodynamic data obtained from the study of this subject are summarized in Figure 7. The results obtained were surprising, since the cardiac output in recumbency was found to be extremely low. The cardiac index was 1.30 L./min./M², a value that is comparable to those we have obtained in the study of severe congestive heart failure and shock. The calculated peripheral vascular resistance was extremely high, indicating intense vasoconstriction in recumbency. When the patient was tilted to 45 degrees the mean arterial pressure fell to almost half of the control value, no significant change occurred in cardiac output, and the calculated

resistance to flow diminished profoundly. The response to metaraminol therapy could not be fully assessed, since the subject was extremely sensitive to it, and its effects made him quite ill. However, one set of values was obtained in recumbency at the height of the response (blood pressure 210/104 mm. Hg). Compared to the control values in the supine position, the most impressive changes were in blood pressure and cardiac output, although the latter was still below the accepted normal values in this laboratory (cardiac index 2.03 L./min./M²).

ANALYSIS OF RESULTS

Venous Return and Cardiac Output. From the study of normal persons, both our data and the data of others [1,3,4] indicate that upon assuming the erect posture the cardiac output may fall as much as 25 per cent. In each patient so studied in our laboratory the cardiac output upon tilting consistently decreased. The maximal normal fall appears to be within the limits of about 25 per cent below resting supine values.

Studies of patients with orthostatic hypotension [4,5,37] indicate that there is sometimes an excessive fall in cardiac output, amounting to as much as 50 per cent of recumbent values. In other subjects with abnormal responses, however, there may be only a moderate fall in cardiac output, a decline which could be considered within normal limits, i.e., less that 25 per cent of supine values. There is a consistent concomitant decrease in stroke volume which is closely related to the fall in cardiac output.

Under ordinary circumstances, normal animals [11] and human subjects are capable of increasing cardiac output sixfold or more when in the recumbent position or when active contraction of skeletal muscle augments venous return to the heart. On the other hand, there is evidence to indicate that man standing motionless in the upright position suffers from a diminished and sometimes inadequate venous inflow to the right atrium. The calculated "central blood volume" in our subjects studied in the recumbent and upright positions diminished as the patient assumed a position deviating from the horizontal, indicating "functional hemorrhage" into the lower part of the body. A 45 degree tilt in normal subjects results in a rise in venous pressure below the level of the heart, and a fall in right atrial pressure amounting to approximately half of the value in the supine position [15]. The administration of large

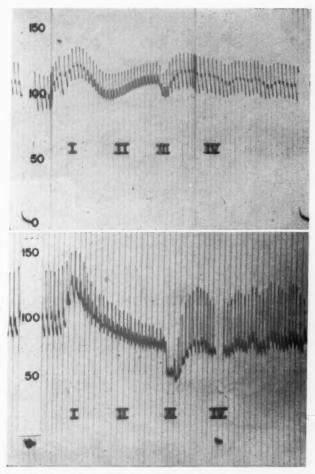


Fig. 5. The effect of the Valsalva maneuver on the intraarterial blood pressure of the normal subject (top) and of patient E. K. (bottom). The patient with postural hypotension fails to have a secondary rise of blood pressure in phases II and IV.

amounts of atropine intravenously in the supine subject results in an increase in cardiac output of 75 per cent above control values: this effect is primarily the result of an increase in heart rate. In subjects who are tilted when given atropine, despite even greater increases in heart rate, the cardiac output is found to increase only slightly, averaging 12 per cent above control values [10]. These results suggest that the limiting factor in the augmentation of cardiac output during tilting is the availability of blood returning from the venous pool.

In summary, therefore, assumption of the upright position results, in normal subjects, in hydrostatic pressure effects exerted on the venous system, with increased venous pressure and volume below the level of the heart, the effect being more pronounced in the most dependent portions of the body. Inferior vena caval inflow and right atrial pressure are decreased, with the

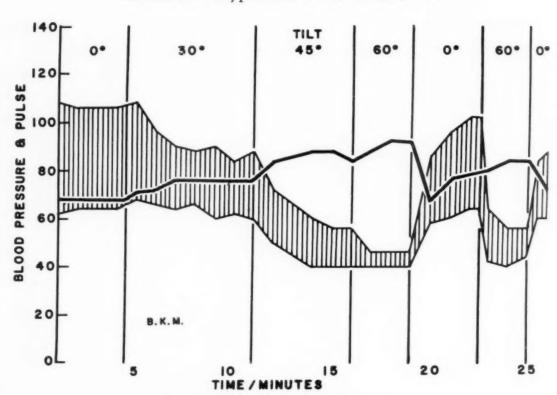


Fig. 6. Tilt table study of subject B. K. M.

result that blood available for maintenance of cardiac output is limited. Reflex mechanisms are brought into play resulting in augmentation of the heart rate, but stroke volume is nevertheless, limited by the availability of blood in the heart and its portals. Venomotor activity undoubtedly plays an important role in the normal subject in assisting venous return in the standing position [44]. Rhythmic alterations in arterial blood pressure during tilting [7] suggest that cardiac filling and/or venomotor tone are phasic phenomena.

In those instances in which cardiac output falls excessively in postural hypotension, it is probable that abnormal venomotor tone is the essential factor related to this malfunction. It has been demonstrated that in patients with orthostatic hypotension the pressure response in isolated vein segments to the Valsalva maneuver, to exercise, cold and hyperventilation is markedly and consistently below the response of normal subjects to the same stimuli [12].

Arterial Pressure and Vascular Resistance. Normal subjects tipped from the horizontal position to a vertical one show a decrease in arterial pulse pressure and an increase in pulse rate. The mean arterial pressure is maintained at supine levels.

Considering the fact that there is a decrease in cardiac output (flow) under these circumstances, the ratio of pressure to flow (resistance) increases. Maintenance of arterial pressure therefore is the result of an increase in resistance to flow, presumably mediated in the arteriolar bed by vasoconstriction. Patients with congestive heart failure show an increase in pulse pressure during tilting and either a fall or no change in pulse rate. Subjects with compensated heart disease have a normal response to tilting [6].

Subjects with orthostatic hypotension are incapable of maintaining normal arterial pressure in the upright position. Systolic and diastolic pressure are both affected. Whether or not the decrease in cardiac output is excessive, an increase in arteriolar resistance fails to occur. When excessive falls in flow occur the patient may be severely compromised by the ensuing extreme hypotension. The assumption is made that there is an abnormality of arteriolar vasoconstrictor mechanisms. Qualitative as well as quantitative data support this concept. It has been demonstrated [14] that in a patient with orthostatic hypotension the central arterial pressure was slightly higher than the peripheral

arterial pressure in the recumbent position, the reverse of what is to be expected in the normal person [8]. During tilting the peripheral arterial pressure exceeded the central pressure, but the difference between the pressures were considerably less than in a normal person. The conclusions drawn from this study are that peripheral vascular "tone" was impaired in this patient in recumbency as well as during tilting.

Examination of the response of the arterial blood pressure to a sustained forced expiratory effort against a pressure head (Valsalva maneuver) in normal subjects and subjects with idiopathic orthostatic hypotension proves interesting. In Figure 5 the arterial pulse tracing of a normal subject and of patient E. K. is reproduced during and following the performance of the maneuver. The components of the curve may be conveniently divided into four phases. Phase I includes the initial rise of pressure, and is presumably due to expression of the pulmonary blood toward the left heart, increasing left ventricular return and output [23]. Phase II, the progressive fall in pressure, is due to a marked depression of cardiac output [24] subsequent to a diminished venous return. Phase III, the abrupt fall in arterial pressure immediately following release of the Valsalva maneuver may be due to momentary absorption of the right ventricular output by the expanding pulmonary vascular bed. Phase IV, the "overshoot" or subsequent rise in pressure, is due to resumption of normal cardiac output into an intensely constricted arteriolar bed. Vasoconstriction is normally mediated during phase II and III by carotid and aortic receptors (and perhaps others), afferent and efferent pathways to and from the vasomotor center and the vasoconstrictor fibers of the sympathetic nervous system. The hypothesis that the overshoot is in part due to an augmented cardiac output from blood "dammed back" in the venous system has been challenged [24] on the basis that cardiac output in normal subjects during this phase was found to be less than or no greater than control values. Under a number of experimental and clinical conditions the overshoot may be diminished or abolished; these include oligemia, the administration of epinephrine, excessive vagal activity, and those conditions which directly affect the sympathetic nervous system, i.e., the administration of ganglionic blocking agents, spinal anesthesia, and lumbodorsal sympathectomy [23]. In the tracing obtained from

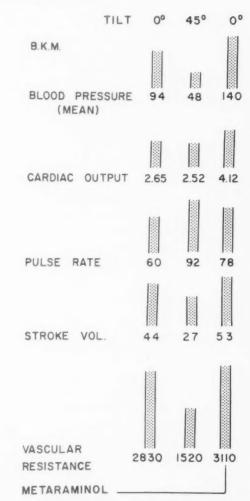


Fig. 7. Hemodynamics of subject B. K. M. The cardiac output is abnormally low even in recumbency. At a 45 degree tilt an impressive fall in stroke volume occurred, but was compensated for by tachycardia. The response to the administration of metaraminol is indicated in the columns on the right.

patient E. K., the overshoot during phase IV is absent, suggesting an abnormality of the baroreceptor organs, the vasomotor center, the sympathetic nerve endings or their secretion, or the neural pathways connecting this complex regulatory system. In this connection Verel [39], in studying three patients with idiopathic orthostatic hypotension, observed that peripheral sympathetic integrity was intact by demonstrating a normal rise in skin temperature with flushing of the skin or blocking the ulnar nerve with local anesthetic. Vasoconstrictor activity following a deep breath, a spinal reflex with efferent sympathetic pathways, was also found to be present. By plethysmographic measurement, however, there was no vasoconstrictor response to cold or painful stimuli applied to the skin, the efferent pathway of which also is

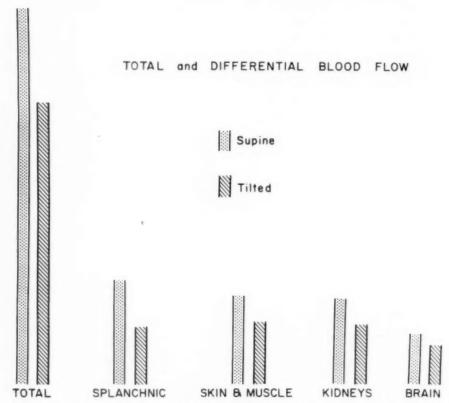


Fig. 8. A synthesis of data compiled from the literature, demonstrating total and regional flow patterns of the normal subject in the supine and tilted positions.

sympathetic. Verel also cited seven patients with orthostatic hypotension from the literature and two of his own who failed to show a change in pulse rate during carotid sinus massage. Eight of the nine patients cited failed to show a fall in blood pressure during massage. These findings were considered significant in that carotid sinus pressure is without effect in only 30 per cent of normal subjects. It was concluded from these data that the anomaly in idiopathic orthostatic hypotension is a lesion above the spinal reflex level, either in the afferent nerves or the central mechanism.

In animals, denervation of both carotid sinuses and section of both aortic nerves results in chronic hypertension and tachycardia. Section of the sinus nerves alone results in similar but temporary changes. It does not seem likely to us that hypofunction of the known baroreceptors or their afferent pathways can be incriminated in this syndrome, for both the carotid and aortic receptors are primarily depressor in action. An insensitive receptor or afferent pathway would be expected to result in a condition the reverse of what is observed in orthostatic hypotension. Capps and deTakats

[13] report on two human subjects in whom orthostatic hypotension developed following bilateral carotid sinus denervation. It should be emphasized, however, that bilateral cervicodorsal sympathectomy had been performed in both patients, and this may have played a decisive role in the dysfunction. One of the patients reported on herein had significant slowing of the pulse in association with the hypertensive phase induced with the administration of metaraminol. (Fig. 2.)

The difficulties encountered in interpretation of calculated peripheral vascular resistance have already been emphasized [5]. Not only are local factors of importance in this expression, but changes in regional flow conditioned by tilting have not been considered. Determination of the magnitude of regional flow to each organ system in intact man is at present an arduous task, and the simultaneous measurement of total and regional flow to all organ systems is impractical. As a matter of interest, however, a synthesis of data from the literature was compiled [4,16–22] and may serve as a rough approximation of total and regional flow in man in the supine and tilted position. Figure 8 summarizes

these data in graphic form. After tilting, there is a decrease in blood flow to all organ systems represented, including muscle and skin, kidneys, the splanchnic bed and the brain. With the exception of the cerebral flow, the circulation in each of these systems decreases out of proportion to the decrease in cardiac output. In the upright position the cerebral arterial pressure, due to gravitational forces, is actually less than in other portions of the cardiovascular system. Although there is a decrease in the cerebral circulation during tilting, the fall is proportionately less than the fall in cardiac output. The cerebral vascular resistance during tilting actually decreases [16]. In the normal man who is standing, therefore, cerebral flow is augmented by a diminished resistance to blood flow, and by the vasoconstrictor responses of arterioles in other portions of the body. These vasomotor responses to a diminished cardiac output are extremely important, however mediated, and are responsible for the adjustments necessary to ensure adequate cerebral metabolism. The symptoms of patients with orthostatic hypotension are directly related to failure of these reflex mechanisms.

Humoral Factors. The vasoconstrictor response of sympathetic stimulation is believed to be mediated by liberation of norepinephrine at postganglionic nerve endings. The urinary excretion of norepinephrine in normal subjects increases over threefold when the subject is tilted to 75 degrees [28]. Luft and Euler [26] and Benestad and Bøe [27] found low twenty-four hour urinary excretions of norepinephrine in subjects with orthostatic hypotension. Although Hickler and his colleagues [30,31] noted high normal plasma norepinephrine levels in patients with this syndrome, they demonstrated that a normal increase in the level failed to occur when the patient was tilted.

A number of questions remain to be answered. Sundin [28] observed a normal increment of urinary norepinephrine during a 75 degree tilt in subjects with orthostatic hypotension. The basal secretion of plasma norepinephrine in these patients is above normal. Solomon and Kuhn [14] demonstrated abnormalities of the central and peripheral arterial pressure pattern in their patient during recumbency, and one of our patients (B. K. M.) had a gross abnormality in cardiac output while lying supine, when plasma norepinephrine values were presumably normal. In patients with essential hypertension

during tilting, a conspiciously low urinary output of norepinephrine [28] and an insignificant rise in plasma levels [32] occurs. Although most patients with this disease are sensitive to vasopressor agents, a case is reported [34] in which the blood pressure could not be maintained in the standing position by continuous intravenous infusion of norepinephrine.

Other poorly defined factors play an essential role in blood pressure regulation. After total extirpation of the thoracic and abdominal sympathetic chains in the dog and cat, the arterial pressure falls abruptly, but then slowly rises to near its original level. After complete ganglionectomy the dog has not only a normal blood pressure but its capacity for work (as illustrated by fighting or running) seems unimpaired [38]. These observations have their counterpart in the long term observation of hypertensive patients subjected to lumbodorsal sympathectomy [40]. Although a striking orthostatic hypotension may occur during the first few weeks or months of the postoperative period, at the end of two years only about half of the patients in this series had a fall in blood pressure of 5 per cent or more in the standing position. A significant fall in systolic pressure following tilting has been observed in hypertensive patients not subjected to sympathectomy [28]. The significance of the renin-angiotensin system [41,42] in this disease is speculative, and to our knowledge assay of angiotensin levels has not been performed. It is of interest that subjects with orthostatic hypotension excrete only a fraction of the normal amount of urinary vasodilator substance [29].

COMMENTS

The most obvious and easily studied manifestation of postural hypotension, orthostatic decline in arterial blood pressure, has naturally received prime consideration in most previously reported cases. In recent years more subtle abnormalities in venous [12] and arterial [14,24] vasomotion have been demonstrated during recumbency, suggesting that a fundamental process of cardiovascular regulation is involved. Tilting the patient is the most efficacious method of demonstrating some of the effects of this basic abnormality, but may not reveal the cardinal features of a comprehensive disorder.

Studies of cardiac output in orthostatic hypotension by others [5] have revealed that it is normal in recumbency, and declines to variable

degrees, sometimes excessively, following tilting. Excessive falls in cardiac output undoubtedly play a significant role in the orthostatic disability, but the major and consistent factor involved is failure of reflex arteriolar constriction. The results of our studies of one patient (E. K.) are in agreement with these observations.

The hydrostatic factors affecting venous return and cardiac output in the normal subject standing have been discussed. These disadvantages are normally partially compensated for by the presence of venous valves, skeletal muscle contraction, and by venomotor activity, regulating venous pressure and resistance [44]. These combined mechanisms play an essential role in the regulation of venous return and cardiac output. Venomotor reactivity is grossly deficient in orthostatic hypotension [12], and it has been shown that cardiac output in this condition can be augmented in the titled position by infusions of serum albumin [5] or the application of a counter pressure garment [37]; a fall in blood pressure may be prevented by application of a blood pressure cuff about both thighs, inflated to above reclining arterial blood pressure, thereby preventing venous pooling in the lower extremities [43]. In the second patient described herein (B. K. M.) the typical failure of reflex arteriolar vasoconstriction common to all other patients studied and reported on was demonstrated. The most interesting and unusual feature, however, was the finding of a distinctly low cardiac output, both in recumbency and during tilting. Although there was no further significant fall in cardiac output observed during a tilt, the maximum degree of inclination tolerated during our studies was only 45 degrees. We believe that the most logical reason for his low cardiac output is virtually complete absence of venomotor activity. The patient had good reason to suspect that "not enough blood was going to the brain" while he was standing, for in the absence of compensatory arteriolar constriction in other organs, the proportion of this low cardiac output entering the cerebral circulation must be low indeed. He had learned, however, to use to advantage the expedient of active muscular contraction as a mechanism to augment venous return to the heart.

The available evidence would serve to support the hypothesis that in idiopathic orthostatic hypotension malfunction of the autonomic nervous system is an essential feature of the disease. The associated occurrence of abnormali-

ties in perspiration and in sexual function which are sometimes present lend further support to this conception. Further, the syndrome may accompany overt nervous system disease, and may follow, at least temporarily, surgical interruption of sympathetic pathways. Abnormalities in plasma levels and urinary excretion of the accepted humoral mediator of sympathetic vasomotion, norepinephrine, have been discussed. The crucial question to be considered is the mechanism by which animals and human subjects, both hypertensive and normotensive, regain vascular tone and reactivity after extensive sympathectomy. This regain in tone occurs after adrenalectomy and hypophysectomy, and if due to increased responsiveness to a vasoconstrictor substance, its source is neither the adrenal or the pituitary [38]. The production of permanent and progressive orthostatic hypotension appears to require something more than interruption of sympathetic pathways beyond the spinal cord. If a heretofore unidentified regulatory mechanism is deficient in this disease, normally it apparently does not require sympathetic integrity beyond the preganglionic fibers; if a humoral agent is involved, its nature and source remain to be identified.

SUMMARY

Case histories and hemodynamic studies of two patients with idiopathic orthostatic hypotension are reported. Both patients demonstrated failure of reflex arteriolar vasoconstriction in response to tilting. The symptomatology and hemodynamic abnormalities were temporarily completely reversed in one of these subjects by the oral administration of metaraminol. The other patient had a distinctly low cardiac output in recumbency which may be presumed to be a consequence of inadequate venous return. Evidence is cited to support the contention that the disease is the result of a basic defect of cardiovascular regulation, manifest in the standing and recumbent positions. Although autonomic nervous system dysfunction may be consistently demonstrated in this syndrome, by presently accepted concepts the circulatory disturbance cannot be entirely ascribed to these abnormalities.

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Circulating Antihuman Kidney Antibodies in Human Renal Disease*

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THE relationship between immunologic phenomena and glomerulonephritis has been well established since Masugi's experimental production of nephritis by antikidney serum 1929 [1]. Other investigators such as Smadel [2], Kay [3] and Seegal [4,5] have confirmed the production of nephritis by means of various antikidney and other antitissue serums. Krakawer and Greenspon [6] have attempted to define the specific antigen producing the nephrotoxic serums in experimental animals and found the highest antigenic activity in glomerular basement membrane fractions. While this experimental nephritis is not identical with human glomerulonephritis, the immunologic implications are similar and the evidence for the relationship of an immunologic reaction in the production of human nephritis is strong. Seegal and Bevans [7] in a recent review discussed this relationship in detail.

The use of serologic methods in studying glomerulonephritis is a logical extension of the theories of its etiology and pathogenesis. In recent years many serologic methods have been utilized to establish some means of establishing prognosis and diagnosis. In a recent review, Fischel [8] divided the serologic methods into two groups. The first is related to the streptococcal etiology of glomerulonephritis and includes demonstration of antibodies to streptolysin O, streptococcal C polysaccharide and streptokinase. The second group of phenomena is related primarily to the presence of autoantibodies to human kidney in the course of the disease. This refers to the mechanism postulated by Schwentker and Comploier [9] who propose that the streptococcal toxin causes damage to

renal tissue and subsequent release into the general circulation of a protein which acts as a "foreign" protein to the reticuloendothelial system, thereby stimulating the production of an antibody to this kidney protein. Lange and his co-workers [10] demonstrated the presence of antihuman kidney (AHK) antibodies in the serum of patients with acute and chronic glomerulonephritis, utilizing the collodion agglutination technic of Cavelti [11]. Liu and McCrory [12], using a hemagglutination method employing tanned red blood cells, also were able to demonstrate the presence of autoantibodies in glomerulonephritis. The presence of an antihuman kidney antibody has been both substantiated [13,14] and denied [15,16], depending on the method of antibody detection used.

The methods employed probably contribute to the variability of results and in fact have caused Lange and his group [17] to discard the collodion agglutination procedure. The production of a polystyrene latex suspension of uniform particle size by the Dow Chemical Company provided a colloid of much greater practicability and renewed our interest in the colloidal agglutination method of approach. This report deals with a modified method of determining the presence of circulating AHK antibodies using such a polystyrene latex suspension.

METHODS AND MATERIAL

Preparation of the Antigen. A 20 per cent suspension of human kidney in 1.1 per cent sodium chloride solution served as the antigen. The kidney is obtained from premature or full term infants within twenty-four hours of death and is processed immediately. The kidneys are minced and washed with repeated

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changes of normal saline solution until the supernatant is free of blood. A suspension is prepared by homogenizing the previously minced kidney in a Virtis 23 homogenizer for five minutes at maximum speed. After homogenization, the supernate is harvested by centrifugation at 3,500 r.p.m. for two to four hours or until clear and then lyophilized in 3 ml. aliquots. A sample of each antigen lot is standardized against a serum of known titer so that all lots of antigen can be adjusted to the same potency. The lyophilized antigen is stable indefinitely when stored at 4°c. It is reconstituted with deionized water just prior to use. Polystyrene latex of uniform particle size (0.81μ) is used as the colloid phase.* The working suspension is obtained by diluting 1 ml. of stock solution with 1.5 ml. of deionized water. It is stable at room temperature but must be protected from freezing. The kidney antigen is adsorbed onto the latex particles by allowing 1 ml. of the reconstituted antigen solution to react with 0.2 ml. of the working latex suspension. After incubating for one hour at room temperature it is then diluted to 10 ml. with a calcium saline diluent. The calcium saline diluent used contains 9.8 gm. of NaCl, 0.15 gm. of CaCl2 and 0.1 gm. NaHCO3 dissolved in 1,000 ml. of deionized water. These concentrations were found by Wagner [18] to be optimal for the binding of the kidney antigen to collodion particles and in our hands were also optimal for the binding of antigen to the latex particles.

The Agglutination System. Serial serum dilutions are made, beginning with a 1:5 dilution, with succeeding dilutions by the doubling method to a final dilution of 1:1280, using the previously described calcium saline diluent. The tubes containing 0.5 ml. of the diluted serum are allowed to stand at room temperature for one hour in contact with 0.1 ml. of the antigen suspension and then are centrifuged at 1,500 r.p.m. for three minutes. The particles are then resuspended and read for agglutination by means of a microscope light or Kahn viewer. A duplicate set of serum dilutions are tested with uncoated latex particles as a control. A saline control is also included with each group of serum dilutions. The last tube showing macroscopic agglutination is taken as the titer. Titers of 1:20 or greater are considered positive.

Patient Material. The patients studied were all inpatients or outpatients of the Medical and Pediatric Services of The George Washington University Medical Division of District of Columbia General Hospital, The George Washington University Hospital, and the Mt. Alto Veterans Administration Hospital. The diagnosis in forty-seven of the patients was established by renal needle biopsy as previously described [19]. In the remaining sixty-eight patients the diagnosis was based on clinical observation and careful examination of the urinary sediment.

* Obtained through the generosity of the Arthritis and Rheumatism Foundation, 10 Columbus Circle, New York, New York. The group of normal subjects consisted of third year medical students and laboratory personnel in whom there was no evidence of renal disease either by history or by clinical and laboratory findings.

RESULTS

Preliminary studies were undertaken to establish the conditions required for reproducible results utilizing latex particles in the agglutinating system. The diluent used was chosen after comparing a group of positive and negative serums in 1.1 per cent NaCl, 0.85 per cent NaCl and the calcium saline diluent previously described. It was found that the most constant titers were obtained with the calcium saline diluent and that there was an absence of nonspecific agglutination. This is in agreement with the data of Singer and Plotz [20] on the characteristics of polystyrene latex particles in various buffer mixtures. Latex particles of three sizes $(0.5, 0.81 \text{ and } 1.1 \mu)$ were tested during the preliminary study. The particles 0.81μ in size were found to give the sharpest agglutination in the experimental tubes while exhibiting no spontaneous agglutination in the control tubes. The 0.5μ particles gave consistently lower titers while the particles of 1.1 μ exhibited spontaneous agglutination in the control tubes.

The effect of complement was investigated by testing five positive and five negative serums both before and after heat inactivation of 56°c. No difference in titer was obtained. As a further check, guinea pig complement was added to the system and again there was no change in titer.

Replicate determinations of rabbit serums of known titer agreed within one tube dilution. No presumed positive serums tested showed agglutination in a dilution less than 1:10. Serial determinations on these positive serums showed at least one sample in which agglutination occurred at a dilution of 1:20 or greater. No presumed normal or negative serums developed agglutination beyond the first tube (1:5 dilution).

Agglutination in a serum dilution of 1:20 or higher was arbitrarily considered as positive.

Serums from 118 patients with renal disease or diseases which might produce demonstrable antibodies were tested for AHK antibodies by means of the latex agglutination method. In addition, the serums from twenty-five young healthy adults were also tested. The results of this study are summarized in Table I. Serums

from fifteen patients were found to have demonstrable titers of AHK antibodies; all fifteen were found in a group of thirty-six patients with glomerulonephritis. One patient who exhibited a positive serum on two occasions came under study because of suspected intercapillary glomerulosclerosis manifested by edema, proteinuria, arterial microaneurysms and diabetes mellitus. A renal biopsy was consistent with acute glomerulonephritis. Four patients with a histologic diagnosis of intercapillary glomerulosclerosis had no demonstrable AHK antibodies.

Of twenty-three patients with histologic evidence of acute glomerulonephritis, nine exhibited positive serums. These nine patients were tested within one month of onset of signs of renal disease.

The group of patients classified as having collagen vascular disease included twelve patients with disseminated lupus erythematosus, two with scleroderma and one with dermatomyositis. Other patients studied included five with streptococcal infections, two with acute rheumatic fever, eight with pyelonephritis, and two with pulmonary tuberculosis. None of the twenty-six serums obtained from these patients revealed the presence of AHK antibodies.

The autoantibody demonstrated by the collodion particle test may represent a false positive Wassermann reaction [8] since the antigen used is quite similar to Wassermann antigen. To test this possible source of error, serums were obtained from twenty-four patients shown to be both qualitatively and quantitatively serologically positive for syphilis. These positive serums were obtained from the serology section of the District of Columbia General Hospital Central Laboratory. No AHK antibody activity could be demonstrated in these serums. Serums were also obtained from patients with febrile illness which could possibly give false positive antibody response. These included two patients with infectious mononucleosis, two with bacterial endocarditis, two with pneumococcal pneumonia, one with infectious hepatitis, and one with serum sickness. None of these eight serums revealed any AHK antibody.

Since only the group of patients with glomerulonephritis exhibited the presence of AHK antibodies an attempt was made to try to correlate the presence and height of titer with the course of the disease. Figure 1 represents the plot of titers against time after onset of symptoms. There appears to be no good correlation between these

TABLE I
DETECTABLE AHK ANTIBODY TITERS

Diamoria	No. of	Total	
Diagnosis	Positive	Negative	Total
Acute glomerulonephritis	9	14	23
Membranous glomerulonephritis	1	2	3
Subacute glomerulonephritis	2	0	2
Chronic glomerulonephritis	3	5	8
Healed glomerulonephritis	0	5	5
Beta-streptococcus infections	0	5	5
Rheumatic fever	0	2	2
Collagen disease	0	15	15
Pyelonephritis	0	8	8
Nephrosclerosis	0	3	3
Leptospirosis	0	1	1
Intercapillary glomerulosclerosis	0	4	4
Toxic nephritis	0	2	2
Acute renal insufficiency	0	2	2
Syphilis and positive STS reactors	0	24	24
Infectious mononucleosis	0	2	2
Infectious hepatitis	0	1	1
Pulmonary tuberculosis	. 0	2	2
Serum sickness	0	1	1
Subacute bacterial endocarditis	0	2	2
Pneumococcal pneumonia	0	2	2
Total patients	15	103	118
Normal young adults	0	25	25

parameters. However, in individual patients there appeared to be some relationship to the course of the disease, as can be seen in Figure 2.

Patient L. V. (indicated by X-X, Fig. 2) presented with a history of migratory arthritis and no urinary tract symptoms. A microscopic examination of her urine revealed the presence of red blood cells and on testing she was found to have an AHK antibody titer of less than 1:20. Subsequent examinations revealed a rise in titer to 1:40 which remained elevated until the twenty-second day of her hospitalization when it became negative. Renal tissue obtained by needle biopsy revealed acute glomerulonephritis.

Patient K. S. (indicated by O-O, Fig. 2) presented with the nephrotic syndrome and on renal biopsy was found to have subacute glomerulonephritis. He was first seen approximately twelve weeks after the onset of his symptoms and at that time exhibited an AHK titer of 1:160. His titer remained at this level until he was started on treatment with 20 mg. of prednisolone daily, at which time it dropped to 1:40. After one week this therapy appeared to be less effective and the patient began to show increasing signs of renal insufficiency. The serum titer obtained at this time was 1:160. The prednisolone dosage was increased to 40 mg. per day and repeated examinations revealed titers of less than 1:20. Despite the development of a negative AHK antibody titer his renal insufficiency be-

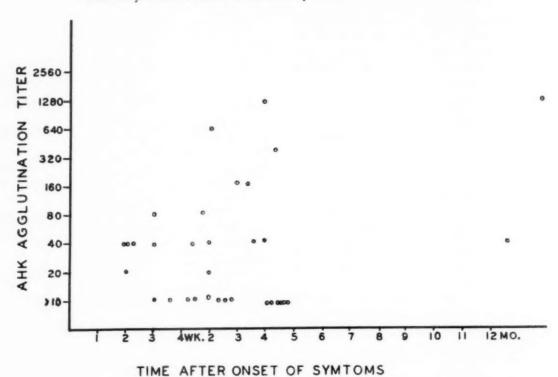


Fig. 1. Titer of AHK after onset of symptoms of glomerulonephritis.

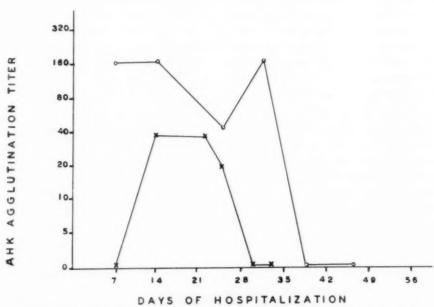


Fig. 2. The relation between clinical course and AHK titer. Patient L. V. indicated by X-X. Patient K. S. indicated by O-O.

came more severe and he died on the forty-fifth day of hospitalization.

In order to be assured of a positive control serum at all times, two rabbits were immunized by intraperitoneal injection of a 20 per cent suspension of human kidney. Both animals were subjected to a series of daily injections for a

period of two weeks. The animals were then allowed to rest for two weeks after which a second course was given. Prior to the first course the animals were bled and the serums were found to be free of AHK antibodies. Two weeks after completion of each course of immunization the animals were bled again and the serums studied

TABLE II
PRODUCTION OF RABBIT AHK ANTIBODIES

Time						
Rabbit 1 control	0					
1st immunization 4 weeks	1:40					
2nd immunization 8 weeks	1:40					
13 weeks	1:40					
11 months	1:40					

by the present technic. In both animals AHK antibody titers of 1:40 developed and persisted until the animals were sacrificed one year later. These data are summarized in Table II.

COMMENTS

The role of autoantibodies in the pathogenesis of glomerulonephritis was suggested by Schwentker and Comploier [9]. Using a mixture of homologous kidney emulsion and streptococcal toxins they were able to produce circulating autoantibodies, demonstrable by complement fixation, in animals so immunized. As a corollary to their work they proposed that an antigen was released from the damaged kidney which became a foreign protein and caused the production of an autoantibody which perpetuated and increased the degree of damage in the kidneys of patients with glomerulonephritis.

This theory has provided impetus for the further investigation of the production of auto-antibodies in human glomerulonephritis. Lange and his co-workers [10], using a modification of the collodion agglutination procedure of Cavelti, were able to demonstrate the presence of circulating AHK antibodies in both acute and chronic glomerulonephritis. Their results revealed higher titers and a greater percentage of positive serums in patients in the more chronic phases of glomerulonephritis and suggest that the continued presence of AHK antibodies may be related to poor prognosis for recovery following an episode of acute glomerulonephritis.

As cited previously, other groups of investigators have had varying degrees of success in demonstrating circulating AHK antibodies. Goodman and Baxter [16] failed to demonstrate AHK antibodies by either the complement fixation method or by the Boyden hemagglutination procedure. Pfeiffer and Bruch [13] found AHK antibodies in patients with progressive chronic

glomerulonephritis using the collodion agglutination technic but not with the complement fixation technic. Their reasons for abandoning the collodion agglutination technic were its lack of reproducibility in individual specimens and the difficulty in standardizing the collodion particles. Our own attempts to use collodion particles encountered the same difficulties that caused Lange to give up the technic. Liu and McCrory [12], using the hemagglutination technic of Boyden, demonstrated results similar to those of Lange and his group in that higher titers and a greater percentage of positive results were obtained in patients with more progressive nephritis and in patients with the nephrotic syndrome. They also demonstrated positive reactions in patients with infectious diseases and rheumatic fever. Cross reactions with antigens from other tissues were noted but were not consistent nor were they related to the height of the AHK antibody titer. Gajdusek [21], using the complement fixation technic, has demonstrated circulating autoantibodies to kidney, placenta and liver in patients with nephritis, lupus erythematosus and infectious hepatitis. He found strong cross reactions between antibodies to kidney and placenta, and obtained positive titers in the serums of patients with lupus erythematosus. Wagner et al. [24] found positive titers to kidney, liver and placenta in a majority of patients with preeclampsia and eclampsia. This is not unexpected considering the similarity between the glomerular lesions of eclampsia and those of membranous glomerulonephritis, and the possibility that both may have a similar pathogenesis.

The presence of AHK antibodies has been suggested by still another technic. Lippman and his co-workers [22] demonstrated an adverse effect on tissue culture explants of rat kidney using serum from patients with glomerulonephritis but no degeneration or growth inhibition during incubation with serum from normal subjects. However, since they studied only serums from patients with nephritis and from normal subjects, non-specific effects due to acute illness cannot be excluded. If their observations were extended to include other diseases of the kidney, acute febrile illness, and collagen diseases with the same results, further evidence for the elaboration of a nephrotoxic antibody would result. In addition, the technic would provide a means of demonstrating the actual cytopathologic effects of the AHK antibody. Krakawer and Greenspon [6] have demonstrated that the greatest antigenic activity rests in the glomerular basement membrane. However, here too there is a mixture of possible antigens which could be responsible for the nephrotoxic effects.

Our data differ from these previous reports in that there have been fewer positive responses in patients with glomerulonephritis, and a higher degree of specificity. This may be related to the fact that different proteins are bound to the colloidal particles with varying pH and electrolyte composition of the diluent used. Wagner [18] found that calcium chloride produced an increase in titer in the collodion particle test. In the latex particle technic calcium ions also seem

to produce the optimum agglutination.

The protein-binding characteristics of the latex particle itself, as compared with those of the collodion particle or the tanned red blood cell, may also account for the differences between our data and those of the previously cited studies. In view of the large number of antigens present in the kidney extract, these characteristics may allow for the greater adsorption of some of the antigens on the different particles used. Thus it has been demonstrated by immunoelectrophoretic procedures [23] that there are at least twelve different antigens present in a crude kidney extract employed in the various technics mentioned. Certainly the variation in results between the various methods could be explained on the basis of one or more of these antigens participating in a given reaction.

Another difference in results between the latex agglutination and the other methods is the absence of positive reactions in patients with disseminated lupus erythematosus. This also may be explained by differences in antigen binding between latex particles and collodion particles. The lack of specificity of the Boyden procedure is probably related to the fact that it is an extremely sensitive agglutination technic

which in turn decreases its specificity.

The data on AHK antibodies cannot be adequately evaluated in their relationship to the pathogenesis of glomerulonephritis until further study of the exact nature of the antigens involved has been completed. The limited data from serial determinations in patients with glomerulonephritis in our series suggest that the presence of a demonstrable AHK antibody titer which does not promptly fall or continues to rise is a poor prognostic sign. In the group of fifteen patients

with glomerulonephritis who exhibited positive titers, three showed a persistant elevation or a rising titer. Progressive and fatal disease developed in all of these patients. Further data on this observation are being gathered in an effort to define more clearly the significance of this finding. Studies directed toward purification and characterization of the antigens involved in the latex agglutination technic and examination of possible cross reactions with antigens of other tissues such as liver, lung and placenta also are in progress. It is hoped that these studies will provide information concerning the role of immune reactions in the pathogenesis of glomerulonephritis.

SUMMARY

A method utilizing polystyrene latex as a colloidal particle for agglutinating antibodies in a study of acute renal disease is presented. The serums from 118 patients with renal disease or diseases capable of producing abnormal serologic reactions and serums from twenty-five healthy young adults were examined for the presence of antihuman kidney (AHK) antibody.

AHK antibodies were demonstrated in fifteen of thirty-six patients with glomerulonephritis. None were found in the normal subjects.

Serial determinations suggest that persistence of an AHK antibody titer is a poor prognostic sign in patients with glomerulonephritis.

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Hypothalamic-Pituitary Sarcoidosis*

A Report on Four Patients, One with Prolonged Remission of Diabetes Insipidus Following Steroid Therapy

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LTHOUGH involvement of the hypothalamus and pituitary body, with diabetes insipidus and/or varying degrees of adenohypophyseal failure, has been recognized in isolated instances of sarcoidosis this association has not been widely appreciated in evaluating patients with hypopituitarism or diabetes insipidus of unexplained etiology. Diabetes insipidus was first reported by Tillgren [1] in 1935 and since then a number of cases have been described [2-14] but in most of them the clinical diagnosis was based solely on the symptoms of polydipsia and polyuria and the finding of a dilute urine. No efforts were made to eliminate hypercalcemia or renal sarcoidosis as causes for these symptoms [15]. Moreover, the diabetes insipidus has been described in some cases as remitting, but the possibility of adenohypophyseal deficiency developing and leading to decreased solute load and fluid exchange has usually not been considered as a reason for loss of polydipsia and polyuria. The diagnosis of adenohypophyseal hypothalamic involvement by sarcoid granuloma has usually been made either at autopsy or during exploratory craniotomy [2-4,10,11,14,16-22]. In only a few instances have adequate studies of endocrine function been carried out and the influence of steroid therapy investigated [12,14,23]. So far no success has been achieved in treating sarcoid of the hypothalamic-pituitary region, but several examples of apparent beneficial response of central nervous system sarcoidosis to steroid therapy are recorded [24-26]. The treatment of hypothalamic-pituitary sarcoid

with adrenal steroid is thus of more than academic interest.

In the present report four instances of Boeck's sarcoid with hypopituitarism and/or diabetes insipidus clinically diagnosed and confirmed by appropriate laboratory studies are described and the response to both replacement and therapeutic doses of corticosteroids recorded. In one case an apparently permanent remission of diabetes insipidus was achieved by steroid therapy, providing strong evidence for the etiology of the hypothalamic lesion. In all four cases, however, the diagnosis of sarcoid involvement of the hypothalamus and/or pituitary body remains presumptive, since the patients are alive and no tissue diagnosis relevant to this involvement is available.

CASE REPORTS

Case I. J. B. (Duke No. E-03254), a forty-four year old married Negro man, was first admitted to Duke Hospital on February 19, 1955, with a fifteen year history of frontal headaches. For three years he had had a crusted post-traumatic ulcer on one finger and for two years a "dry" non-pruritic skin eruption of the face. He also complained of impotentia and hoarseness. For one year he had had polydipsia and polyuria, with frequency twelve times per twenty-four hours. Five weeks before admission he began to have morning vomiting without nausea. He also had mild tinnitus, slightly decreased auditory acuity, and had had a transient episode of right amblyopia. Elsewhere, two months before admission, a lumbar puncture revealed cerebrospinal fluid which contained 22 cells per cu. mm. and 310 mg. per cent protein.

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The patient appeared chronically ill but well nourished on admission. The blood pressure was 135/80 mm. Hg, pulse 84 and temperature normal. Positive findings included dull mentality; a waxy, umbilicated, papular skin eruption over the upper part of the body and arms; raised, crusted skin lesions on the left elbow and first left metacarpal; enlarged, non-tender submandibular lymph nodes; old chorioretinitis in the right fundus; and edematous vocal cords. Neurologic examination showed diminished auditory acuity with air conduction greater than bone conduction, absent vibratory sensation over the left medial malleolus and a slight limp with incomplete circumduction of the right foot. The rest of the physical examination was within normal limits.

The hemoglobin was 15 gm. per cent, hematocrit 45 per cent, white blood count 2,600 cells per cu. mm. with a normal differential count. The erythrocyte sedimentation rate was 36 mm. per hour. Sternal bone marrow showed slight erythroid hyperplasia. The urine had a specific gravity of 1.003 but was otherwise within normal limits. Chemical analysis of the blood revealed fasting blood sugar of 90 mg. per cent, non-protein nitrogen 29 mg. per cent, cholesterol 230 mg. per cent, total protein 7.7 gm. per cent with 4.7 gm. per cent albumin and 3 gm. per cent globulin, calcium 9.7 mg. per cent, phosphorus 4.3 mg. per cent, alkaline phosphatase 1.7 Bodansky units, uric acid 2.9 mg. per cent, carbon dioxide combining power 33.9 mEq. per L., chloride 99.8 mEq. per L., sodium 147.8 mEq. per L. and potassium 4.1 mEq. per L. The result of the blood serologic test for syphilis was negative. Cerebrospinal fluid showed an opening pressure of 145 mm. and a closing pressure of 90 mm.; there were no cells, and results of an India ink examination were negative. The cerebrospinal fluid protein was 1,238 mg. per cent, sugar 43 mg. per cent, and colloidal gold 5555554322; the result of the serologic test for syphilis was negative. The reaction to old tuberculin (1:100) and Frei skin tests was negative. The electroencephalogram was normal. I131 uptake by the thyroid was 30 per cent per twenty-four hours (normal 15 to 45 per cent). A roentgenogram of the skull revealed no abnormalities. The chest roentgenogram revealed prominent hilar shadows. Pulmonary function test showed slight ventilatory restriction.

Visual fields were normal. An audiogram showed 20 to 40 per cent loss "mixed type." A Hickey-Hare test [27] showed a baseline urine flow of 7.7 cc. per minute, with specific gravity of 1.001. After intravenous infusion of 780 cc. 2.5 per cent saline solution the urine flow was 14 cc. per minute (specific gravity 1.001), and 6 cc. per minute (specific gravity 1.004) in subsequent thirty and forty-five minute intervals. On another day, after no fluid intake for seventeen hours, the urine flow was 2 cc. per minute (specific gravity 1.002); and after 0.2 unit aqueous Pitressin® given intravenously, the urine flow fell to less than 1 cc. per minute (specific gravity 1.014). The

highest specific gravity observed without Pitressin treatment was 1.009. When fluid intake was unrestricted his urine output ranged between 6 and 10 L. per twenty-four hours.

A biopsy specimen of a waxy facial lesion showed a "granuloma lesion representing an epithelioid tu-

bercle, compatible with Boeck's sarcoid."

While in the hospital the patient was given 25 units of ACTH daily by eighteen hour intravenous drip for ten days. After the third day there was general subjective improvement. The patient reported his first erection in several months and during the remainder of his stay in the hospital he had daily erections. Following his discharge, however, impotentia returned. A repeat lumbar puncture on the last day of treatment with ACTH showed cerebrospinal fluid protein of 90 mg. per cent. He was discharged on March 11, 1955, with instructions to take cortisone acetate, 25 mg. four times a day, potassium chloride, Amphogel, and a low sodium diet. On April 6, 1955, a repeat Hickey-Hare test showed a baseline urine flow of 5.6 to 8 cc. per minute (specific gravity 1.003 to 1.010); and after the administration of 780 cc. of 2.5 per cent saline solution the flow fell to 4 cc. per minute, then to 2 cc. per minute (specific gravity 1.008 to 1.010) in subsequent thirty minute intervals. The patient reported no polyuria or polydipsia, felt stronger and the skin lesions on the face had cleared. On April 26, 1955, withdrawal of cortisone treatment over a three week period was initiated. Five months later he was readmitted with joint pains, anorexia, and vesicular skin lesions on the forehand. However, the diabetes insipidus had not recurred. He was able to concentrate urine to a specific gravity of 1.021 after seventeen hours of water deprivation. Cerebrospinal fluid protein was 330 mg. per cent. A pneumoencephalogram showed mild cortical atrophy. Treatment with cortisone was reinstituted. In subsequent follow-up, treatment was switched to prednisone, 5 mg. four times a day, and then to 5 mg. twice a day. In March 1957 his cerebrospinal fluid protein was 125 mg. per cent. Prednisone therapy was discontinued and 9-alpha-fluorohydrocortisone substituted in order to perform an ACTH test. This showed a baseline urinary excretion of 8.9 mg. of 17-ketosteroids [28] and 4 mg. of 17-hydroxycorticosteroids in twentyfour hours. Following the intramuscular injection of 40 U.S.P. units of ACTH gel the urinary 17-ketosteroid excretion rose to 53.2 mg. per twenty-four hours and 17-hydroxycorticosteroid excretion to 50.3 mg. per twenty-four hours, demonstrating actively functional adrenal tissue. Urinary gonadotropin assay measured 3 rat uterine units per twenty-four hours (normal 2 to 8 rat uterine units in adult male) [29]. Repeat chest x-ray examination was within normal limits. On subsequent prednisone treatment he continued as before except for development of glaucoma, with progressive visual loss, in November 1958.

The patient continues to complain of impotence but

no longer has any symptoms of diabetes insipidus. On a recent visit in June 1959, after not having had steroid therapy for several months, he was found to have actively progressing skin lesions, exudates in both fundi and bilaterally pale discs. He appeared chronically ill. Spinal fluid protein was 290 mg. per cent. His urinary excretion of 17-ketosteroids was 4.1 mg., of 17-hydroxycorticosteroids 1.3 mg. per twenty-four hours, and of gonadotropin less than 2 rat uterine units. I¹³¹ uptake was 7 per cent in twenty-four hours, and the serum cholesterol 365 mg. per cent and there was delayed relaxation of the deep tendon reflexes. On a Hickey-Hare test he was able to decrease his urine flow from 6 cc. per minute (specific gravity 1.004) to 0.5 cc. per minute (specific gravity 1.009) and on partial fluid restriction (890 cc. per twenty-four hours) his urine specific gravity was 1.014. Dexamethazone therapy was begun with marked subjective improvement and some clearing of the skin lesions and the exudates in the fundi when last seen in September 1959.

Comment: This patient presented with headaches, a skin eruption, loss of potentia and diabetes insipidus. Sarcoid was demonstrated on skin biopsy and a striking elevation of cerebrospinal fluid protein was also found. On appropriate doses of ACTH and later of cortisone, his diabetes insipidus cleared and so far has not recurred during a four year follow-up. This would suggest that a lesion involving the hypothalamic-hypophyseal tract had been favorably influenced by steroid therapy. For several years no definite failure of gonadotropic, corticotropic or thyrotropic functions was demonstrable by the tests employed, but recent observations suggest that ACTH, thyrotropin and gonadotropin deficiency might now be developing despite the steroid therapy. It could not be established initially whether his complaints of impotentia reflected the more non-specific consequences of chronic illness or those of specific hypothalamic or adenohypophyseal involvement by sarcoid. The restoration of potentia during ACTH therapy probably was a non-specific response to his general feeling of well-being consequent to this treatment.

CASE II. H. W. S. (Duke No. D-29204), a sixteen year old white boy, was referred to Duke Hospital for a check-up on December 17, 1951. Pernicious anemia had recently developed in his nineteen year old sister and the patient was referred for hematologic study. Although growth and development had been normal until age ten, he had not grown in height since then and pubescence had not been initiated.

On admission he appeared four to six years younger then his stated age. His height was 60 inches, blood pressure 105/70 mm. Hg, pulse 80 per minute, respirations 18 per minute and temperature normal. His skin was coarse. There were small, shotty axillary and cervical lymph nodes. The liver was palpable 1 to 2 cm. below the right costal margin, and the spleen 2 to 4 cm. below the left costal margin. There was no axillary or genital hair and the penis and testes were prepuberal in development. The remainder of the physical examination was non-contributory.

The hemoglobin was 13.6 gm. per cent and the white blood cell count 9,500 cells per cu. mm. with a normal differential. The sternal bone marrow was normal. The urine had a specific gravity of 1.026 and was otherwise negative. The reaction to a blood serologic test for syphilis was negative. There was no retention of bromsulphalein in forty-five minutes. Gastric analysis showed no free hydrochloric acid before or after an injection of histamine. The basal metabolic rate was -9 per cent. The serum cholesterol was 150 mg. per cent. Urinary gonadotropin excretion was less than 1 rat uterine unit per twenty-four hours and 17-ketosteroids measured 4.5 mg. per twenty-four hours. Roentgenograms of the abdomen, chest and skull revealed no abnormalities. Bone age was delayed by approximately two years.

No endocrine therapy was given as it was thought that he was exhibiting simple delayed pubescence. On August 27, 1952, his height was 61 inches and urinary gonadotropin excretion was 1 rat uterine unit per twenty-four hours. There was still no evidence of pubescence. An insulin glucose tolerance test [30] was normal. On April 28, 1953, urinary gonadotropins measured 3 rat uterine units per twenty-four hours and urinary 17-ketosteroids 2.1 mg. per twenty-four hours. On March 8, 1954, urinary gonadotropins were 2 rat uterine units per twenty-four hours, 17-ketosteroids 1.9 mg. per twenty-four hours, and still no pubescent changes had occurred. Because of this he was given a six week course of treatment with 1,000 I.U. of chorionic gonadotropin (APL®) intramuscularly every two days. By the end of this course of therapy, pubic hair had appeared and he was having ejaculations once per week producing 1 to 2 drops of ejaculate. A seminal examination on July 14, 1954, however, revealed azoospermia.

On October 10, 1955, the boy's height had increased to 66¾ inches (span 70: upper measurement 32 inches, lower measurement 33 inches). A twenty-four hour I¹³¹ uptake by the thyroid was 14.7 per cent (normal 15 to 45 per cent). The bone age was slightly delayed, as before. Urinary gonadotropin excretion was less than 2 rat uterine units per twenty-four hours, urinary 17-ketosteroids measured 2.9 mg. per twenty-four hours and 17-hydroxycorticosteroids 2 mg. per twenty-four hours. On June 7, 1956, he complained of a painful mass over a distal interphalangeal joint. Microscopic sections of this showed large aggregates

of granulomatous tubercle-like reaction without caseation which were interpreted as sarcoid. Fungus and acid-fast stains were negative. Urinary 17-hydroxycorticosteroid excretion was 0.8 mg. per twenty-four hours and 17-ketosteroids 4.5 mg. per twenty-four hours. On December 10, 1956, the reaction to an old tuberculin skin test (1:10000) was negative; protein-bound iodine was 6.8 μ g. per cent; and the response to a water load test [31] was normal.

On February 11, 1957, the boy was readmitted for further study. Lumbar puncture was negative, with a cerebrospinal fluid protein concentration of 25 mg. per cent. Chest roentgenograms showed bilateral hilar masses consistent with sarcoidosis. Roentgenograms of the skull were non-contributory. A testicular biopsy specimen showed no normal Leydig cells. The tubules were normal in size with moderate peritubular fibrosis. The vast majority of tubules showed only spermatogonia with a few primary spermatocytes. The remaining tubules showed at best three layers of germ cells including a few secondary spermatocytes. No spermatids or spermatozoa were seen. Sertoli cells were present but in "poor" condition.

Radioactive vitamin B₁₂ absorption was normal. The total serum protein was 7.9 gm. per cent with 5.1 gm. per cent albumin and 2.8 gm. per cent globulin. Serum calcium was 10.1 gm. per cent and phosphorus 5.8 mg. per cent. Fasting blood sugar, non-protein nitrogen, serum sodium, potassium, chloride, carbon dioxide combining power and alkaline phosphatase were all within normal limits. Urinary 17-hydroxycorticoids were 2.6 mg. per twenty-four hours and 17-ketosteroids 4.3 mg. per twenty-four hours. Urinary gonadotropins were less than 1 rat uterine unit per twenty-four hours.

The patient was discharged receiving a depot testosterone* preparation, 200 mg. administered intramuscularly every three weeks. By October 30, 1957, he had shown increased growth and masculinization, and androgen treatment was changed to fluoxymesterone,† 5 mg. per day. At that time, urinary 17-hydroxycorticosteroids were 0.5 mg. per twenty-four hours and 17-ketosteroids 3.8 mg. per twenty-four hours. On December 30, 1957, he complained of weakness and lack of libido. Treatment with cortisone acetate, 12.5 mg. every eight hours, was started and the dose of fluoxymesterone was discontinued. The height was 6914 inches. The patient then moved to Tennessee and was seen by Dr. Grant Liddle I at Vanderbilt University who reported that the patient was given 30 mg. hydrocortisone a day during the summer of 1958 without significant subjective benefit. After androgen therapy had been dis-

* Kindly supplied as Delatestryl® by Dr. E. C. Reifenstein, E. R. Squibb & Sons, New York, New York.

† Kindly supplied as halotestin by Dr. C. J. O'Donovan, The Upjohn Company, Kalamazoo, Michigan.

‡ We wish to express our gratitude to Dr. Liddle for allowing us to report some of his data.

Table 1
PITUITARY ADRENAL FUNCTION TESTS (CASE II)

Date	Therapy	Urinary 17-Hydroxy- cortico- steroids (mg./24 hr.)	Urinary 17-Keto- steroids (mg./24 hr.)
October 31	None	6.7	6.7
November 1	None	7.7	6.0
November 2	SU 4885;* 500 mg. every 4 hr.	10.4	5.9
November 3	None	11.6	7.1
November 4	ACTH: 50 units intrave- nously over 8 hr. period	38.0	13.9

* 2-methyl-1, 2-bis-(3-pyridyl)-1-propanone.

continued for three months the urinary FSH excretion was less than 6.6 mouse units per twenty-four hours. Fluoxymesterone therapy was then reinstituted. Hydrocortisone therapy was discontinued on October 1, 1958 and the patient was admitted to Vanderbilt Hospital in November where pituitary adrenal function studies were made; the results are recorded in Table 1.

These data were interpreted as showing normal adrenocortical function but less than normal capacity of the adenohypophysis to secrete ACTH in response to SU 4885, an inhibitor of 11β -hydroxylase [32]. Other studies performed at Vanderbilt Hospital revealed normal blood chemical determinations and a negative reaction to an old tuberculin 1:100 skin test.

Subsequent follow-up at Duke in February and May 1959, revealed no change in his clinical status. A specific gravity of a urine specimen taken at random was 1.023. The serum cholesterol was 190 mg. per cent.

Comment: This patient showed evidence of partial failure of anterior pituitary secretion of gonadotropin and ACTH. The diagnosis of sarcoid is well substantiated but it cannot be established with assurance that sarcoidosis in fact existed at the time the patient was first observed. Without histologic proof, one cannot be certain of the presence of a sarcoid lesion in the hypothalamic-pituitary area. Nevertheless, a strong inference seems justified that such a lesion exists and has been responsible for the endocrine manifestations.

In light of the absence of diabetes insipidus, it seems probable that the lesion responsible for the symptoms of pituitary disease is located within the sella turcica but involvement of centers in the hypothalamus controlling gonadotropin and corticotropin secretion cannot be ruled out. The persistently normal spinal fluid protein might be used as evidence against brain involvement.

CASE III. H. L. K. (Duke No. D-77453), a twenty-one year old single Negro man, was first seen at the Duke Medical Center Outpatient Clinic on November 16, 1953, with a three months' history of anorexia, nausea and vomiting, leg cramps and postural dizziness. Four weeks prior to admission he had had severe recurrent vomiting with hematemesis. He lost 63 pounds during these three months.

The patient appeared chronically ill but not emaciated despite the weight loss. His blood pressure was 110/70 mm. Hg, pulse 68 per minute, temperature 37°c., weight 169 pounds, height 71 inches. There was no axillary hair and the pubic hair was gynecoid in distribution. The testes were small and soft. The remainder of the physical examination was noncontributory. The hemoglobin was 13.1 gm. per cent, white blood cell count 5,350 cells per cu. mm. The urine had a specific gravity of 1.020 and was otherwise negative. Results of serologic tests for syphilis were negative. The serum calcium was 8.4 mg. per cent and phosphorus 3.2 mg. per cent. The serum total protein was 7.3 gm. per cent with 4.6 gm. per cent albumin and 2.7 gm. per cent globulin.

The patient did not return for additional studies and was next seen one year later. By that time his weight had dropped to 102 pounds. A history was elicited of several tarry stools, transient diplopia, absent libido and potentia, increased urinary frequency and volume and nocturia three to four times per night. Examination now revealed marked emaciation. The blood pressure was 100/70 mm. Hg, pulse 72. There were small epitrochlear and inguinal lymph nodes and, as before, small testes.

The hemoglobin was 11.4 gm. per cent and the white blood cell count 7,050 cells per cu. mm. with a normal differential. The urine had a specific gravity of 1.008, but was otherwise negative. Chemical analysis of the blood revealed fasting blood sugar 99 mg. per cent, non-protein nitrogen 25 mg. per cent, calcium 8.7 mg. per cent, phosphorus 3.4 mg. per cent, carbon dioxide combining power 31.2 mEq. per L., sodium 151.9 mEq. per L., potassium 3.7 mEq. per L., total protein 9.1 gm. per cent with 5 gm. per cent albumin and 4.1 gm. per cent globulin. Results of a serologic test for syphilis were negative. Stool guaiac was negative. The reaction to old tuberculin 1:10000, histoplasmin, blastomycin and coccidioidin skin tests was negative. The electrocardiogram showed juvenile T wave pattern. The electroencephalogram was within normal limits. Lumbar puncture showed normal pressure, 22 mononuclear cells and 4 polymorphonuclear cells, protein 164 mg. per cent and sugar 43 mg. per cent. A chest roentgenogram showed calcified right hilar nodes. The roentgenograms of the skull and long bones revealed no abnormalities. Bone age films were interpreted as being consistent with the chronologic age. A pneumoencephalogram was within normal limits. Twenty-four hour I131 uptake by the thyroid was 18 per cent, the

basal metabolic rate was -33 per cent and serum cholesterol was 147 mg. per cent. The response to a water load test was abnormal with inadequate diuresis. The urinary 17-ketosteroid excretion was 2 mg. per twenty-four hours. A Hickey-Hare test showed no antidiuretic response to hypertonic saline solution but a prompt one to the intravenous administration of Pitressin. Visual fields and acuity were normal.

The diagnosis of panhypopituitarism and diabetes insipidus of unknown etiology was made. Although one consultant suggested sarcoidosis, further diagnostic studies were not pursued. In November 1954 replacement therapy with 25 mg. cortisone, 45 mg. desiccated thyroid, 15 mg. methyl testosterone and 5 mg. Pitressin tannate in oil was started. He improved markedly on this therapy and was discharged. By January 26, 1955, he had gained weight to 148 pounds and was working on a farm ten to twelve hours per day without difficulty. He showed progressive androgenization after the dose of methyl testosterone was increased to 30 mg. daily. However, a few months later a draining sinus developed in the right deltoid region and extended to the axilla at an injection site of Pitressin tannate in oil.

On February 6, 1956, he was readmitted to Duke Hospital for further studies. His weight was 173 pounds. Routine laboratory data were within normal limits. Culture of secretions from the draining sinus grew out Staphylococcus albus and hemolytic streptococcus. Fungus and acid-fast cultures were negative. The reaction to a repeat old tuberculin skin test 1:100 was negative. A biopsy specimen taken from the region of the sinus showed only a chronic granulomatous reaction of undetermined etiology; a lymph node biopsy specimen was within normal limits. The serum sodium, potassium chloride and carbon dioxide combining power were within normal limits. The serum cholesterol was 240 mg. per cent. Two weeks after discontinuing cortisone therapy the urinary 17-hydroxycorticosteroid excretion was 2.6 mg. per twenty-four hours and 17-ketosteroids 5.3 mg. per twenty-four hours with rises to 4.9 mg. per twenty-four hours and 8.6 mg. per twentyfour hours, respectively, after the administration of ACTH. At the end of twenty-four hours of water deprivation, the urine concentrated to a specific gravity of 1.016. The patient was discharged taking testosterone, isoniazid, Gantrisin® and posterior pituitary powder by nasal insufflation.

On follow-up March 22, 1956, the draining sinus had healed and the isoniazid and Gantrisin treatment was discontinued. In April 1957 the serum protein-bound iodine was 4.3 µg. per cent. In August 1957, the urinary 17-hydroxycorticosteroids measured 1.4 mg. per twenty-four hours and 17-ketosteroids 5.9 mg. per twenty-four hours. In another effort to make a positive diagnosis a right epitrochlear lymph node biopsy was performed. This specimen revealed "focal

tubercles, granulomatous lymphadenitis with scarring necrosis and giant cells, compatible with Boeck's sarcoid." On September 15, 1958, urinary gonadotropins were again less than 1 rat uterine unit per twenty-four hours. Cortisone and testosterone replacement therapy was reinstituted. Subsequently, because of cold intolerance and a serum cholesterol of 298 mg. per cent, treatment with desiccated thyroid was instituted but there was no definite symptomatic change following this. When last seen the patient was using Pitressin tannate in oil three times a week and posterior pituitary powder by nasal insufflation two to three times a day on Sundays, with fair control of polydipsia and polyuria, and was able to do heavy farm work without difficulty. Because the patient lives at some distance and returns to the clinic only at infrequent intervals, it has not been practical to attempt treatment with large doses of steroids.

Comment: Initially this patient presented evidence of diabetes insipidus and hypopituitarism, characterized by gonadotropin, corticotropin and probably thyrotropin failure. It was not until four years later that the diagnosis of sarcoid was finally established. In retrospect, the association of cachexia and panhypopituitarism should have suggested the possibility of a systemic disease such as sarcoid as an etiologic factor. It seems probable that, if sarcoid is responsible for the endocrine manifestations, it involves the stalk of the pituitary to account for both diabetes insipidus and panhypopituitarism. Unfortunately, no opportunity to treat the sarcoid with corticosteroids has been available.

CASE IV. J. A. (Duke No. F-6197), a white girl aged thirteen years and five months, was first admitted to Duke University Medical Center on August 21, 1959, complaining of loss of vision in the left eye of three and a half weeks' duration. After a normal pubarche and thelarche, menarche occurred in July 1958, with normal, cyclic menses until she missed one period in October 1958. Subsequently menses returned and were cyclic until the abrupt onset of amenorrhea three months prior to admission. At the latter time she first noted persistent nocturia, and one month before admission frank polydipsia and polyuria appeared. For about four weeks she had had recurrent bifrontal headaches for which her physician prescribed analgesics and "one thyroid pill" daily. Three and a half weeks before admission she suddenly lost vision in the left eye, was found to have a massive left vitreous hemorrhage and was treated with prednisone in tapering doses. For two days the patient had had nausea, occasional vomiting and a feeling of tightness in the lower substernal region. Two months before admission her weight reached 150 pounds, but on

voluntary dieting this had dropped to 128 pounds. The remainder of her general medical history and endocrine review of systems were non-contributory. The family history was positive only in that a maternal aunt and first cousin had diabetes mellitus.

The temperature was 37°c, pulse 80, respirations 18, blood pressure 110/70 mm. Hg lying, 100/72 mm. Hg standing. The height was 65 inches, weight 128 pounds. The patient was a well developed and nourished white girl who did not appear ill. The skin was clear, and there was no lymphadenopathy. Examination of the right eye revealed a visual acuity of 20/15 with a generalized constriction of the visual field, normal tension, keratitic precipitates beneath the cornea, severe venous engorgement and marked papilledema with one white exudate below the macula. In the left eye vision was limited by a massive vitreous hemorrhage to light perception only. Axillary and pubic hair were normal, the breasts well developed. The uterus was borderline small, the vagina poorly estrogenized.

The hemoglobin was 15 gm. per cent, white blood cells 9,000 per cu. mm. with 9 to 14 per cent eosinophilia on smear. L.E. cell preparation was negative. The result of a bone marrow examination was normal except for a minimal increase in plasma cells and eosinophilic precursors. Routine urinalyses were within normal limits except for persistently low specific gravity. The reaction to skin tests including old tuberculin 1:100, blastomycin, coccidioidin and histoplasmin was negative. The following blood chemical determinations were within normal limits: fasting blood sugar, blood urea nitrogen, electrolytes, calcium, phosphorus and alkaline phosphatase. Serum total proteins were 7.4 gm. per cent with 3.7 gm. of both albumin and globulin. The serum cholesterol was 218 mg. per cent, protein-bound iodine 6.2 μg. per cent. The urinary 17-hydroxycorticoids were 5.3 and 17-ketosteroids 8.1 mg. per twenty-four hours, both within normal limits. Urinary gonadotropins were 3 rat uterine units, a normal value.

The following observations confirmed the presence of diabetes insipidus: (1) persistent excessive fluid exchange of 3 to 5 L. daily, (2) persistent urinary hypotonicity after twelve hours of water deprivation, and (3) an abnormal reaction to a Hickey-Hare test characterized by failure to respond to the intravenous administration of hypertonic saline solution but with a brisk, normal response to intravenously administered Pitressin.

Stereo roentgenograms of the skull did not show any abnormalities; the sella turcica was intact. A lumbar puncture revealed an opening pressure of only 130 mm. water, 8 lymphocytes per cu. mm., and a spinal fluid protein of 76 mg. per cent. A few days later the spinal fluid findings were confirmed, and spinal oxyencephalograms were within normal limits. Fluoroscopy and roentgenograms of the chest revealed bilateral hilar adenopathy. A left pre-scalene

fat pad biopsy specimen contained lymph nodes which histologically were compatible with sarcoidosis; they were completely replaced by numerous non-caseating granulomas in which many giant cells of the Langhans' type were noted; acid-fast and periodic acid-Schiff stains revealed no bacteria.

On August 30, 1959, prednisone therapy with potassium supplement was begun at a dosage of 40 mg. daily; this has been slowly tapered to her current maintenance dose of 7.5 mg. daily. On a clinic visit November 12, 1959, the headaches had subsided, there was considerable decrease in venous engorgement and papilledema of the right eye, but no resorption of the left vitreous hemorrhage. The diabetes insipidus responded well to Pitressin tannate in oil administered subcutaneously. Her first vaginal bleeding in six months occurred from November 4 to 8 and resembled a normal menstrual period; subsequently she has had two additional consecutive periods.

Comment: The diagnosis of sarcoidosis has been well established in this adolescent girl. An intracranial hypothalamic sarcoid lesion could readily explain the elevated spinal fluid protein and diabetes insipidus. The same lesion could account for amenorrhea with loss of hypothalamic control of cyclic gonadotropic secretion, although the illness itself could equally well be responsible for the temporary interruption of menses. There were no clinical or laboratory evidences of TSH deficiency, but unfortunately she had been taking small doses of desiccated thyroid for one month prior to study. The latter medication was discontinued, and two and a half months later she remains clinically euthyroid. There was no detectable impairment of ACTH secretion. After careful neurosurgical study the papilledema could not be attributed to increased intracranial pressure; we suspect that it arose from retro-orbital sarcoidosis with partial venous occlusion. The severe left vitreous hemorrhage is also worthy of note.

COMMENTS

The four cases cited illustrate some of the difficulties in the recognition of sarcoidosis as a basis for hypothalamic and/or pituitary disease. When the diagnosis of the sarcoidosis is obvious, as in Cases I and IV, there is no problem in relating a manifestation such as diabetes insipidus to involvement of the hypothalamus by the basic disease. On the other hand, when systemic involvement by sarcoid is not very widespread, is not accompanied by such characteristic findings as hyperglobulinemia, and the

endocrine manifestations appear early in the disease, the correct diagnosis may be elusive. This was the problem in two of our cases.

Furthermore, the evidence that the neurologic or endocrine signs are in fact due to sarcoid may be most difficult to obtain short of postmortem examination. Otherwise, the diagnosis must remain presumptive even when permanent remission is achieved by steroid therapy. In the latter instance, however, the probability of the correctness of the presumption is certainly very considerable.

The diagnostic difficulties are illustrated well by a patient recently seen by one of us (C. N. S.) with a suprasellar mass demonstrated by pneumoencephalogram, bitemporal hemianopsia, adenohypophyseal insufficiency and sarcoid of the dermis on biopsy, with the presumptive diagnosis of sarcoid involving the hypothalamicpituitary area. The patient was treated with predisone. However, progressive visual field changes occurred and hence a craniotomy was performed after a month's observation. Unexpectedly, a suprasellar meningioma was found which was successfully removed. This experience emphasizes the importance of clinical vigilance and judgment in the management of patients diagnosed as having hypothalamic-pituitary sarcoidosis not confirmable by direct examination of the involved tissue.

The long interval between the development of the first symptoms and signs of endocrinopathy and the recognition of systemic sarcoidosis in two of our cases emphasized the need for alertness to this diagnosis in unexplained cases of hypopituitarism and diabetes insipidus. One case has been reported with hypopituitarism secondary to sarcoidosis in which the endocrine manifestations had been present for twenty-four years before the diagnosis was proved by autopsy [21]. In both our cases there were clues to the correct diagnosis when the patient was first seen, but these were not pursued. One patient (Case II) had generalized lymphadenopathy and hepatosplenomegaly. Only later did the characteristic hilar lymphadenopathy become recognizable on the chest roentgenogram. The other patient (Case III) likewise exhibited generalized lymphadenopathy. This together with his race and geographical origin and the presence of an unexplained systemic disease with hypopituitarism and cachexia should have stimulated an immediate intensive search for diagnostic evidence of sarcoidosis.

The importance of establishing this diagnosis is emphasized by the successful treatment of our first case. This patient has achieved a prolonged and perhaps permanent remission of diabetes insipidus following corticosteroid therapy. Despite this, other manifestations of the disease have relapsed and he has required repeated courses of steroid therapy for these. The evidence for remission is based not only on the subjective relief of symptoms but also, more critically, on the restoration to normal of the response to infusion of hypertonic saline solution and the ability to concentrate his urine during prolonged water deprivation. We have not been able to locate any other similarly documented example of either spontaneous or steroid-induced recovery from diabetes insipidus due to sarcoid. Disappearance or decrease in polyuria and polydipsia has been noted, but these are not adequate criteria on which to conclude that the diabetes insipidus has remitted. Thus, for example, the diabetes insipidus was reported as improved in Barber's case [2] because polyuria disappeared, but the urine specific gravity was only 1.006. Furthermore, it is well known that polyuria and polydipsia may disappear when adenohypophyseal insufficiency develops, even though the basic disturbance of diabetes insipidus persists, i.e., an inability to excrete urine more concentrated than plasma [33]. Examples of steroid-induced recovery of sarcoidosis of the brain [25], spinal cord [26] and retina [34] have been recorded. However, it should be emphasized that since sarcoid is a disease subject to spontaneous remissions one can never have complete confidence that specific therapeutic measures were in fact responsible for the responses [40].

It is noteworthy that Pennell [13] in a review of fifty-four case reports of central nervous system sarcoidosis found that 35 per cent of the patients had diabetes insipidus. Neurologic manifestations of diverse sorts are not uncommon with sarcoidosis and may mimic a number of disorders, including brain tumor [10,13,19, 35,36]. Since diabetes insipidus occurs most commonly in association with other neurologic manifestations, it is well to be on the alert for the development of this syndrome in patients known to have sarcoidosis of the nervous system.

All our patients with diabetes insipidus showed increases in cerebrospinal fluid protein, one (Case I) to an extraordinary level (1,238 mg. per cent). Pennell [13] previously reported

consistent elevations in cerebrospinal fluid protein in patients with sarcoidosis of the central nervous system but not in those in whom the lesions were limited to the pituitary gland. Our patient with hypopituitarism but no diabetes insipidus had a normal spinal fluid protein. It would seem a reasonable (but unproved) assumption that when signs and symptoms of hypopituitarism occur with sarcoidosis, the lesion is intrasellar when the spinal fluid protein is normal. Conversely, an elevated spinal fluid protein might denote hypothalamic involvement. Only the opportunity to examine postmortem material and perhaps the application of some of the newly developing tests of pituitary function [32] will confirm the validity of this suggestion.

Sarcoidosis of the pituitary gland is not always associated with signs and symptoms of hypopituitarism, as is apparent from the report of Bleisch and Robbins [3], who reviewed the cases reported up to 1952 and added four of their own. This is not surprising, since it is well known that almost complete destruction of the gland is necessary before overt manifestations of insufficiency become apparent. In many cases the sarcoid lesion consists of localized granulomas without complete destruction of the gland. Commonly, lesions may be localized predominantly in the stalk of the pituitary and extend into the hypothalamus [4,7,14,16,21], leading to atrophy of the adenohypophysis as well as diabetes insipidus. In general, incomplete hypopituitarism might be anticipated with such lesions. It would not be surprising if our third patient (Case III), who had hypopituitarism and diabetes insipidus, were found to have these pathologic changes. Clinical recognition of hypopituitarism due to sarcoid should occur more frequently with improvement in the technics for evaluating adenohypophyseal and hypothalamic function.

Treatment of the hypopituitarism due to sarcoid should follow the same principles of substitution for deficiencies as with other causes of hypopituitarism. This is being done in our cases, with excellent results. In addition, however, it would seem desirable to attempt treatment with large doses of adrenal steroids [37–39] to establish whether the sarcoid lesion might be amenable to this treatment. Since such treatment is associated with considerable risk it should be undertaken only with the patient under careful medical supervision. Unfortu-

TABLE II SALIENT CLINICAL FEATURES

Case No.	Prominent	Duration of Illness Before	Hypothalamic-Pitui-	Inferred Locus of	Maximal Cerebro- spinal Fluid Protein (mg. %)	Serum Protein (gm. %)		
	Presenting Symptoms	I harrosis of tary Functional Loss	tary Functional Loss	Lesion		Total	Albu- min	Globu- lin
1	Headaches, polyuria and polydipsia	2-3	Antidiuretic hormone	Hypothal- amic	1,238	7.7	4.7	3.0
п	Delayed puberty	5+	Gonadotropin, adreno- corticotropin	Intrasellar	28	7.9	5.1	2.8
Ш	Nausea, vomiting weight loss and pos- tural dizziness	4	Antidiuretic hormone, gonadotropin, adreno- cortitropin, thyro- tropin	Hypothal- amic and intrasel- lar	164	9.1	5.0	4.1
IV	Headaches, visual loss, polyuria and polydipsia	3/12	Antidiuretic hormone	Hypothal- amic	76	7.4	3.7	3.7

nately, two of our patients live at great distances from the hospital and return only at infrequent intervals and hence we have been reluctant to attempt this therapy. Possibly pituitary insufficiency may be developing now despite steroid therapy, but this remains to be established.

Magnus [23] treated two patients with pituitary hypofunction due to sarcoid with large doses of ACTH. Although there was improvement in the systemic manifestations of the disease and the patients had a considerable feeling of well-being, no convincing objective evidence of improvement in endocrine function was presented. One of us (C. N. S.) has recently seen a patient at the Boston Veterans Administration Hospital with panhypopituitarism, a suprasellar mass demonstrated by encephalogram, incomplete bitemporal hemianopsia, mild left hemianopsia and increased spinal fluid protein in whom all endocrine and neurologic manifestations disappeared during cortisone therapy. Unfortunately, no histologic diagnosis of sarcoid was made, but this diagnosis seems very likely.

Table II summarizes the salient clinical features of the four cases and indicates the presumed site(s) of the sarcoid lesions.

SUMMARY

Four cases of sarcoidosis with hypothalamic and/or pituitary gland hypofunction are presented. The spectrum of manifestations has been discussed and inferences as to the site of the lesions offered. The importance of searching for

sarcoid in cases presenting as idiopathic hypopituitarism and/or diabetes insipidus is stressed. Elevated cerebrospinal fluid protein, without other prominent cerebral symptoms, occurred in three patients all of whom had diabetes insipidus. This finding may be of considerable diagnostic value. Regression of diabetes insipidus occurred in one patient treated with steroids.

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Arteritis in Rheumatoid Arthritis*

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In some patients with classic rheumatoid arthritis features develop in the course of their illness which are indicative of a more generalized disease. This systemic process has taken the form of disseminated rheumatoid granulomas and vascular lesions; it has been referred to as "rheumatoid disease" [16,64] or "malignant rheumatoid arthritis" [6]. In a disease of unknown cause and obscure pathogenesis, it has been difficult to understand the precise relationship of these complications to the primary disorder. Further knowledge about them, however, may shed light on the nature of the basic disease process.

In this report patients with rheumatoid arthritis in whom arteritis developed were investigated to elucidate the relationship of this finding to other aspects of their illness, including treatment and ultimate course. The patients with arteritis are compared to others with a similar syndrome collected from the literature.

HISTORICAL REVIEW

Arteritis in General. The first report dealing with generalized arterial inflammation was that of Kussmaul and Maier [42] in 1866. They described the clinical and postmortem findings of two patients with polyarteritis nodosa, ascribing the symptoms to grossly visible nodules along the medium-sized arteries of the viscera. Over the next sixty years infrequent reports of similar cases appeared. More recently there has been a tendency to regard arteritis as a manifestation of diverse diseases rather than as a disease entity unto itself [80]. In 1926 Von Glahn and Pappenheimer [76] described arteritis in ten of

forty-seven patients with rheumatic fever. They believed that these vascular lesions could be distinguished from those of typical polyarteritis nodosa because the affected arteries, usually smaller vessels, did not contain thrombi and had not undergone aneurysmal dilatation. Friedberg and Gross [22] reported in 1934 that four of eight patients with widespread visceral involvement by polyarteritis nodosa showed, in addition, the lesions of rheumatic fever; typical Aschoff bodies were found in the myocardium.

Experimental production of alterations in blood vessels occurred in the course of studies involving hypersensitivity. Gruber in 1925 [25] suggested that polyarteritis might represent a systemic hyperergic reaction caused by a variety of agents to which the vessel wall had become sensitized. By repeated injections of horse serum, Klinge [40] produced lesions in rabbits which he considered similar to those of rheumatic fever and noted concomitant vascular lesions that he thought resembled those of polyarteritis nodosa. Clinical expression of these experimental findings awaited the description by Clark and Kaplan in 1937 [12] of vascular changes in two patients who died with serum sickness following treatment of pneumococcal pneumonia. Rich [56] confirmed the presence of arteritis in serum sickness in man and also noted the association of such lesions with sulfonamide hypersensitivity clinically and experimentally. He suggested that there was a similarity of these experimental lesions to those found in rheumatic fever, polyarteritis nodosa, lupus erythematosus and the rheumatoid subcutaneous nodule.

The early descriptions of polyarteritis nodosa have been extended so that now a more de-

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tailed picture of this syndrome has emerged. A striking feature in many reports [7,27,34,38,46, 50,60] has been a high incidence of neurologic symptoms, particularly peripheral neuritis. This is thought to result from vascular occlusion of the nutrient artery to the peripheral nerve [36].

Arteritis in Rheumatoid Arthritis. In recent years the systemic nature of the disease process in rheumatoid arthritis has been documented by several studies [3,5]. Alterations have been noted in almost all viscera, in muscle and in nerve, in addition to the well recognized changes in joint structures and subcutaneous tissue. The rather specific granuloma, the prototype of which occurs in the subcutaneous nodule with its center of fibrinoid material surrounded by a palisading layer of histiocytes, has been identified in many tissues. It has not always been possible to recognize the true nature of longstanding lesions which, on healing, leave nonspecific scars. Study of the heart in rheumatoid arthritis has suggested to some investigators a greater than chance incidence of valvular lesions of the type caused by rheumatic fever, but Sokoloff's [68] and Mainland's [47] careful pathologic and statistical studies cast some doubt on this. It is clear, however, that pericarditis is not uncommon in rheumatoid arthritis and that a specific rheumatoid granulomatous type of valvulitis and mural endocarditis can occur [14,68]. The pathogenesis of these lesions is unknown but the primary role of an inflammatory lesion involving small vessels in the initiation of these granulomas has been suggested by Sokoloff et al. [69,70].

In 1951 Sokoloff, Wilens and Bunim [71] reported upon the incidence in this clinic of vascular lesions in peripheral muscles of patients with rheumatoid arthritis; five of fifty-seven patients were found to have arteritis. Necrosis of the vessel wall was not seen and only arteries of small size were affected. Clinical evidence of extra-articular involvement, beyond that seen in most patients with rheumatoid arthritis, was not described. Since only muscle and, in some instances, subcutaneous nodules were biopsied, it was not possible in their pathologic examination to assess the full extent of the process. Four of their cases have been traced and a follow-up report on them is included in this report. Other patients with rheumatoid arthritis and varying degrees of systemic arterial disease have been reported, many of them recently (Table x1 with accompanying references). It would appear that

vascular inflammation may well be a significant part of the pathology of rheumatoid arthritis.

MATERIAL AND METHODS

Patients. All thirty-four patients in this study were personally studied by us. They represented all patients with rheumatoid arthritis under our care in whom muscle biopsy was either obtained or advised. The great majority were followed on the wards and in the arthritis clinics of the Third (NYU) Medical Division of Bellevue Hospital. Observations were recorded over a period of from two to fourteen years. Most patients were re-examined during 1957 and 1958. All data concerning the patients' histories were recorded during those years. The diagnosis of "classic" rheumatoid arthritis was established for all cases according to the criteria of the American Rheumatism Association [58,59] with the exception of four patients (Cases 17, 21, 29 and 31) who were classified as having "definite" rheumatoid arthritis. It is not possible to estimate the frequency of proved arteritis in patients with rheumatoid arthritis under our care because selection of cases for biopsy was not truly random. It does, however, appear to be uncommon.

Methods. Routine blood and urine examinations were performed by conventional technics in the hospital laboratories and in the laboratory of the Rheumatic Diseases Study Group. The serum rheumatoid factor was detected by the sensitized sheep cell agglutination test using the serum euglobulin fraction for the agglutination and inhibition procedures [82]. The two-hour clot technic was used for the L.E. test [83]. Muscle biopsy specimens were taken from various sites, most of them from gastrocnemius muscle. However, if the patient had signs of peripheral neuritis the biopsy specimen usually was taken from the muscle supplied by the involved nerve. With a few exceptions when it was performed several months later, the surgical procedure was carried out within several weeks after the onset of suggestive symptoms. Usually a block of muscle between 0.5 and 1 cc. was obtained. In most cases the tissue was fixed in 10 per cent neutral formalin for an hour and then in Zenker's solution (containing neither acid nor formalin) overnight, washed and embedded in paraffin. The entire block was sectioned at 6µ and every fifth slide was stained with hematoxylin and eosin. In appropriate instances intervening slides were subsequently stained with connective tissue or elastic tissue stains. The pathologic interpretation was made independently of the clinical appraisal. The diagnosis of arteritis was made only when inflammatory cells could be detected within the wall of the affected artery. Necrosis was considered to be present when markedly eosinophilic "fibrinoid" material and nuclear fragments were seen within the arterial wall. In a few instances necrotic lesions that had healed were identified by the presence of scars and capillaries in the vessel wall.

TABLE I DISTRIBUTION OF PATIENTS WITH RHEUMATOID ARTHRITIS BY CLINICAL FINDINGS

Case No.	No. of Patients	Arteritis on Biopsy	Prominent Clinical Symptoms
1-10	10	Present	Peripheral neuritis
11-13	3	Present	Multisystem disease
14-17	4	Present	None
18-20	3	Absent	Peripheral neuritis
21-23	3	Absent	Multisystem disease:
24-31	8	Absent	None
32-34	3	Biopsy refused	Peripheral neuritis

RESULTS

Of the thirty-four patients of the present study (Table 1), three with peripheral neuritis (Cases 32, 33 and 34) in whom arteritis was suspected clinically refused permission for biopsy and are not considered further except in discussion of the symptom of peripheral neuritis. Of the thirty-one patients who were biopsied, arteritis was noted in seventeen and was not found in fourteen. Data from these patients are presented in the following manner: Various features of these cases are recorded in tabular form with brief case histories of each of the seventeen patients (Cases 1 to 17)

with proved arteritis and of the three patients (Cases 18 to 20) with neuritis but no detectable arteritis. After this, findings in the group with demonstrable arteritis are compared to the group without arteritis. Finally, data from our patients with arteritis are contrasted with those that have been reported in the literature.

It was of interest to evaluate the accuracy with which a diagnosis of arteritis had been made clinically because of the onset of either peripheral neuritis or other clinical evidence of disseminated disease. There were seventeen patients with such symptoms, and arteritis was later proved in eleven (Cases 1 to 8, 11 to 13) but was not found in six (Cases 18 to 23). Findings that were considered to be indicators of a disseminated disease included five instances of pericarditis and single instances of valvular heart disease, pulmonary fibrosis, pleurisy, abdominal crisis, papilledema of the optic nerve, undiagnosed disease of the central nervous system manifested by gross tremors and amyloid disease. No unusual manifestations of rheumatoid arthritis were present in ten patients (Cases 14, 15, 24 to 31) and therefore arteritis was not diagnosed. These were biopsied at random from the population attending the clinics. In eight of these ten no arteritis was detected; in two, unsuspected vascular disease was found. Finally, four patients with arteritis are included in whom no prior

TABLE II CLINICAL FEATURES IN SEVENTEEN PATIENTS WITH RHEUMATOID ARTHRITIS AND ARTERITIS

Case No.	Sex	Age at Onset of Rheumatoid Arthritis (yr.)	Stage of Disease*	Sub- cutaneous Nodules	Epi- scleritis	Hyper- tension	Peri- carditis	Duration Arthritis Before Biopsy (yr.)	Steroid Therapy Before Biopsy (mo.)	Type of Arteritis	Presen
1	F	55	3	+	+	±	0	6	10	Necrotizing	Died
2	F	46	4	+	+	+	+	11†	74	Necrotizing	Died
3	M	31	3	+ 1	0	0	+	26	20	Necrotizing	Living
4	F	60	2	0	0	0	0	1	8	Necrotizing	Living
5	F	45	4	+	+	0	0	15	0	Necrotizing	Living
6	F	44	3	0	+	0	0	11/2	12	Necrotizing	Living
7	F	22	3	+	0	0	0	7	40	Necrotizing	Living
8	F	50	3	+	0	0	0	8	24	Necrotizing	Living
9	M	34	1	+	0	0	+ 1	2	0	Non-necrotizing	Living
10	F	44	3	+	0	+ 1	0	6	0	Non-necrotizing	Living
11	F	25	4	+	+	0	+	32	In past‡	Necrotizing	Living
12	M	51	3	+	0	+	0	6	5	Non-necrotizing	Died
13	M	52	2	+	0	+	+ 1	9	33	Non-necrotizing	Died
14	M	54	3	+ 1	0	± 1	0	5	0	Necrotizing	Living
15	M	64	2	+	0	0	0	5	34	Necrotizing	Living
16	M	42	3	+ 1	0	0	0	11	0	Non-necrotizing	Living
17	F	63	3	0	0	0	0	3/2	0	Non-necrotizing	Died

Note: + = symptom present; 0 = symptom absent; ± = symptom present occasionally

Stage of rheumatoid arthritis according to classification by the American Rheumatism Association [72].

† Earlier biopsy specimen without arteritis obtained three years after onset of arthritis.

Corticosteroids used for unknown duration two to four years previously.

clinical impression of vascular disease had been made. These patients, from the series of Sokoloff, Wilens and Bunim [71], were subsequently noted to have peripheral neuritis in two instances (Cases 9 and 10); in the other two (Cases 16 and 17) no systemic disease was found. Thus, while some patients with arteritis escaped clinical detection, it was possible to select with fair accuracy those patients in whom vascular lesions had developed. As will be noted later, this was especially true if the artery had undergone necrosis. Of the various findings before biopsy that had been thought to be signs of underlying arteritis, only peripheral neuritis and pericarditis were found to be related; the remaining findings were infrequent and present in patients both with and without arteritis. It was subsequently noted on review of the records that episcleritis and subcutaneous nodules were found with increased frequency in patients with arteritis although their presence was not considered significant at the time.

Arteritis and Peripheral Neuritis (Cases 1 to 10). In ten patients symptoms of peripheral neuritis developed and arterial inflammation was evident on muscle biopsy. (Tables II and III).

Case 1. This patient, a widowed, white seamstress, was first seen in 1952 at the age of fifty-nine. (Fig. 1.) In the past she had had pulmonary tuberculosis that became arrested and Graves' disease treated by partial thyroidectomy. She was told of hypertension at age fifty-five. Menopause occurred at age fifty-two. At age fifty-five pain developed suddenly in the left shoulder and lasted several months. She recovered completely but three years later, at age fifty-eight, multiple peripheral joints became painful and

TABLE III
LABORATORY DATA IN SEVENTEEN PATIENTS WITH
RHEUMATOID ARTHRITIS AND ARTERITIS

Case	Rheumatoid Factor (Euglobulin Agglutination)*	L.E. Factor	Hemoglobin (< 12 gm. %)	Protein- uria
1	112	0	+	0
2	224	0	+	0
2 3	+8	0	+	0
4	896	0	0	±
5	112	0	+	0
6	112	+	0	±
7	56	+++000	+	± + 0
8	224	+	+ 0	0
9	14	0	0	0
10	0†	0	+	$\frac{\pm}{0}$
11	56	+	+	0
12	448	0	+	0
13	224	N.P.	0	0
14	+‡	N.P.	0	0
15	112	0	+	0
16	N.P.	N.P.	+	0
17	+‡	N.P.	0	0

Note: + = test positive; 0 = test negative; \pm = test variable, often negative; N.P. = test not performed.

* Highest titer of each patient expressed as the reciprocal of the greatest dilution that caused agglutination.

† Patient in complete remission at time of test.

‡ Results of hemolytic streptococcal agglutination test positive on whole serum [49].

§ Results of capillary latex test positive on whole serum [74].

swollen, but after several months these subsided without specific medication.

When she was first seen in 1952 the arthritis had flared again. Results of the sheep erythrocyte agglutination test were strongly positive and of the

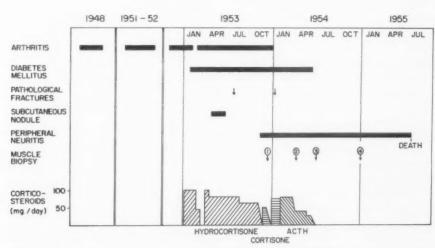


Fig. 1. Case 1. Clinical course. Rheumatoid arthritis with peripheral neuritis and arteritis.



Fig. 2. Case 1. Paralysis of forearms with wrist drop due to peripheral neuritis.

L.E. cell test negative. Because of persistent and severe symptoms, the administration of hydrocortisone was begun at 100 mg. a day in January 1953. She had considerable relief of symptoms. After six weeks diabetes was discovered, and insulin was prescribed. Six months after the onset of steroid therapy she suffered pathologic fractures of the left sixth, seventh and eighth ribs and the seventh thoracic vertebra. Ten months after beginning hydrocortisone therapy she suddenly became disoriented. Her family physician reduced the dose of hydrocortisone from its maintanence level of 60 mg. daily to 20 mg. per day and the joint symptoms became much worse. A week later she noted clumsiness and numbness in her left hand and fingers, followed rapidly by weakness of the left forearm causing wrist drop. She was re-admitted to Bellevue Hospital with paralysis of the left arm. The patient received no steroids for the first three hospital days. Because of increasing arthritic symptoms, cortisone therapy was begun at 50 mg. a day. Rapid improvement of joint symptoms occurred but there was no change in the paralysis. By the fifth hospital day a similar paralysis developed in the right hand and forearm, and diminished pain sensation was noted in a stocking distribution in the lower part of her legs.

Examination of spinal fluid on four occasions showed no abnormalities. On x-ray examination, a new compression fracture of the first lumbar vertebra was noted. By the end of two weeks there had been rapid progression of symptoms; the patient showed bilateral wrist drop, bilateral foot drop and diminished sensation in her hands and feet. (Fig. 2.) Reflexes were absent at the ankles and knees and left biceps. Other areas of the nervous system were free of involvement and there was no subsequent evidence of progression of neuritis.

A biopsy specimen of gastrocnemius muscle was obtained during the third week. Acute necrotizing

arteritis involving small arteries was seen, indistinguishable from that of polyarteritis nodosa. (Fig. 3.)

During the next several months, the patient remained confused. Phenylbutazone, corticotropin and

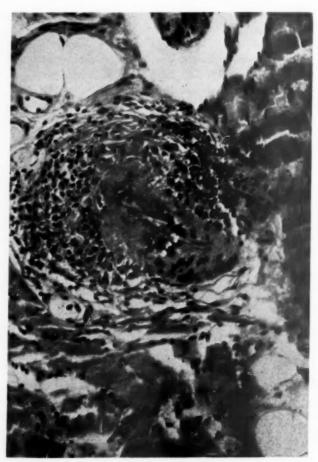


Fig. 3. Case 1. Necrotizing arteritis in a small artery of gastrocnemius muscle; hematoxylin and eosin stain.

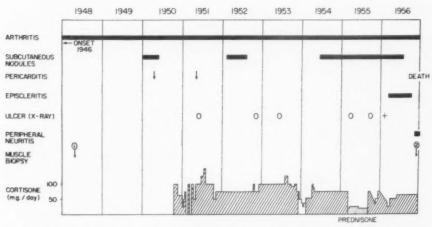


Fig. 4. Case 2. Clinical course. Rheumatoid arthritis with peripheral neuritis and arteritis.

cortisone were administered in sequence during this time and then discontinued. After the fourth month she gradually returned fully to her previous level of alertness. The muscle weakness which had resulted in quadriplegia remained unchanged and sensation in her distal limbs did not return. Her arthritis was no longer acute. Pyuria due to Bacillus proteus followed several bladder catheterizations. Two subsequent biopsies of the gastrocnemius muscle were performed five and seven months after the onset of the neuritis. In both, progressive healing of the arteritis was seen.

After nine months of hospitalization she was transferred to Goldwater Memorial Hospital. She led a sedentary existence there with no change in muscle status. Episcleritis involved both eyes during this time. A fourth muscle biopsy in December 1954 revealed no evidence of arteritis.

In July, 1955, her temperature rose to 105°F. and she went into shock. Despite vigorous measures, the patient died. At autopsy,* extensive, severe, acute pyelonephritis was found. Focal mononuclear inflammatory exudates were seen in the endocardium and aortic intima. The only evidence of vascular disease that could be found was a healed arteritis in a small periadrenal artery. No lesions were seen in serial sections of several blocks of skeletal muscle taken at autopsy.

Comment: In this patient with classic rheumatoid arthritis diabetes and pathologic fractures developed while she was receiving hydrocortisone therapy. Shortly thereafter necrotizing arteritis with severe peripheral neuritis resulted in quadriplegia. Four biopsy specimens were obtained over a period of a year after the onset of peripheral neuritis. The last three demonstrated progressive healing of the lesion so that at autopsy, twenty months after its first ap-

* Through the courtesy of Dr. Herbert Kayden, tissue specimens obtained at autopsy were made available to us.

pearance, there was no evidence of active vascular inflammation. Therapy with corticosteroids and corticotropin had been resumed between the first and third biopsies. Despite healing of the arterial lesions, the paralysis did not improve, presumably because irreversible damage to the involved nerves had already occurred; however, no progression of the peripheral neuritis took place after the second biopsy which showed healing of the arteritis.

Case 2. This patient, a white housewife, was first seen in 1948 at the age of forty-nine. (Fig. 4.) Menopause was uneventful at age forty-seven. Her previous health was good. Veneral disease was denied although results of routine serologic tests for syphilis in the past had sometimes been positive. At age forty-six, arthritis of multiple peripheral joints gradually developed. A muscle biopsy of the gastrocnemius was performed in April 1948 and is included as one of the negative biopsies in the study of Sokoloff, Wilens and Bunim [71]. Splenomegaly was noted in 1949. She received several courses of gold therapy. In March 1950, corticosteroid therapy was begun and continued almost without interruption until her death.

She experienced several episodes that were diagnosed clinically as pericarditis in 1948, 1950 and 1951. On two occasions electrocardiographic changes consistent with this diagnosis were noted. In 1955, signs of hypercortisonism led to a temporary reduction of dosage from previous levels of 75 to 100 mg. cortisone daily to 25 mg. a day. During this reduction, episcleritis and uveitis developed. Because of epigastric complaints, roentgenograms of the stomach and duodenum were taken on five occasions between 1951 and 1955; all were normal. In 1955, a large gastric ulcer was disclosed. Despite these complications, therapy was continued because the patient was not able to endure her arthritic complaints without continued corticosteroid medication.



Fig. 5. Case 2. Portion of sciatic nerve with necrotizing arteritis and thrombosis of accompanying artery; hematoxylin and eosin stain.

In December 1956, numbness and paresthesia in the left foot were noted. Within a few days similar changes occurred in the right foot and the patient could no longer stand. A diagnosis of peripheral neuritis secondary to arteritis was made and confirmed by a biopsy specimen taken from the left anterior tibial muscle. Severe necrotizing arteritis was noted throughout the specimen. The patient became rapidly worse. Numbness occurred on the right half of the face. She had two episodes of acute dyspnea within several days and died in January 1957.

At autopsy necrosis and inflammation of many small arteries were seen in the heart, pancreas, kidneys, uterus, small intestine, peritoneum, periarticular tissue, sciatic nerve and various skeletal muscles. Most of the arterial lesions were healing or healed, with fibrosis of portions of the arterial walls. In addition to widespread arteritis, this patient had extensive involvement of the dermis of several areas of the forearm by lesions resembling subcutaneous nodules of rheumatoid arthritis. Similar rheumatoid granulomas were found in the juxta-articular periosteum of the knee and in the epicardium. Arteritis involving the vessels supplying the sciatic nerve is shown in Figure 5.

Comment: It is of interest that a muscle biopsy performed in the third year of this patient's illness, prior to steroid therapy, revealed no evidence of vascular disease. In the eleventh year of her illness a gross neurologic disorder developed and widespread arteritis was found. Her death was attributed to this fulminating process. Healing of her necrotizing arteritis was observed at autopsy although the patient had continued to receive corticosteroids until her death.

CASE 3. The family history of this white male college administrator included rheumatoid arthritis in his mother and ankylosing spondylitis in an older brother. His own rheumatoid arthritis began about 1931 or 1932, at the age of thirty-one, and involved his hands, knees and feet. Treatment consisted of fever therapy, aluminum injections and gold injections in two courses. The second course of gold was interrupted because of dermatitis. About 1949 the arthritis remitted spontaneously.

When the patient was first seen by us in February 1953 rheumatoid arthritis was moderately active. There was no swelling but deformities were present involving several metacarpophalangeal and interphalangeal joints, the wrists and left knee. Nodules were present in a thickened left olecranon bursa. On April 7, 1954, the patient was admitted to University Hospital because of precordial pain on deep respiration and effort. Electrocardiograms showed progressive changes consistent with the diagnosis of pericarditis. A biopsy specimen of gastrocnemius muscle, which was not sectioned serially, was reported to be normal.

The patient was discharged on April 14, 1954, and convalesced at home, becoming asymptomatic by June 1954. About mid-January 1955 there was a reactivation of his rheumatoid arthritis involving both knees, the fingers and the right wrist. After a month this subsided. In mid-November 1955 there was again activity of the same joints and he was started on prednisolone therapy, 15 mg. daily, which was slowly reduced to 7.5 mg. daily. Throughout 1956 the dose ranged from 7.5 to 10 mg. per day. About January 1957 the dose was raised to 15 mg. daily, but failed to control his symptoms satisfactorily. In June 1957 he complained of pain in the calf muscles on walking, and

increased fatigability; the arthritis continued active. The pain in the calf muscles grew progressively worse until in August 1957 he was unable to walk a block without pain.

On August 26, 1957, he was admitted to the University Hospital for a biopsy of gastrocnemius muscle which now showed focal necrotizing arteritis.* With confirmation of this diagnosis, reduction of prednisolone was begun and he was started on large doses of aspirin and chloroquin. He was discharged home on September 4, 1957. On September 9 he had paresthesias of the left foot and right hand. On September 16 anesthesia was noted in the right median nerve distribution and on the sole of the left foot. On September 23 bilateral foot drop was noted. On September 27 partial bilateral median nerve paralysis appeared. Following this no further neurologic lesions were observed. Several areas of superficial gangrene measuring from 3 to 15 mm. in diameter appeared on the lower part of his legs during the period of neuritis. The patient was intermittently febrile. Anemia developed which was unresponsive to oral and intramuscular administration of iron, vitamin B₁₂ and liver extract. There was nausea, vomiting, progressive weight loss and increased activity of the arthritis. About December 1 the patient began to improve. There was some restoration of sensation in the hands but no improvement of the foot drop or median nerve paralysis has occurred one year after their onset.

Comment: This patient with persistent, moderately severe rheumatoid arthritis experienced an attack of pericarditis in the twenty-third year of his disease, at which time a muscle biopsy specimen showed no evidence of arteritis. Subsequently the arthritis became more severe and corticosteroid therapy was begun. About nineteen months later arteritis became clinically apparent and on muscle biopsy was shown to be of a necrotizing type. Peripheral neuritis of all four extremities developed, with resultant paralysis and little evidence of recovery one year after onset. Small necrotic skin lesions also appeared on the legs.

Case 4. Rheumatoid arthritis developed in this sixty-two year old white woman† in September 1956 when she was sixty years old; it began with involvement of the second metacarpophalangeal joints of both hands, and spread rapidly to the other joints of the hands and shoulders, temporomandibular joints and the cervical spine. Cortisone therapy was begun early in the disease in doses of 150 mg. daily. In

* We were able to examine these sections through the courtesy of Dr. Maurice Richter.

† For permission to study this patient we are indebted to Dr. Thomas' Almy and Dr. Albert Erdman of the Second Medical Division, Bellevue Hospital Center. February 1957 a painful ecchymotic area appeared spontaneously on the right calf and disappeared in two weeks. In June 1957 cortisone was changed to corticotropin. Three days later, while walking, she suddenly fell and found that she could not lift her right foot. About one hour later there was severe pain in the right leg. By that night both legs were covered with red blotches from the knees down.

The patient entered a hospital in another city for eleven days and left in about the same condition but with less severe pain. Three days later at home she experienced sudden pain in the left calf and found that she was unable to dorsiflex the left foot. She entered the Second Medical Division of Bellevue Hospital on September 8, 1957, with bilateral foot drop and corresponding reduction in sensation. A muscle biopsy performed on September 18, 1957, revealed arteritis without necrosis; however, the walls of several arteries which no longer were actively inflamed contained scars suggestive of organized necrotizing arteritis. In March 1958, corticosteroid therapy was very slowly reduced, then stopped. Since then she has been maintained on aspirin with considerable relief of pain. There has been slow but definite improvement in the foot drop.

Comment: In this patient arteritis developed, confirmed by muscle biopsy, and peripheral neuritis with bilateral foot drop only nine months after the onset of rheumatoid arthritis and about eight months after the start of corticosteroid therapy. Associated with the peripheral neuritis were severe calf pain and widespread ecchymoses over the lower part of her legs. Although the muscle biopsy specimen was obtained only about three months after the onset of peripheral neuritis, the necrotic areas in the arteries examined had healed.

Case 5. The patient, a married Negro woman, was first seen in June 1956 at the age of sixty-one for progressive weakness of several months' duration. Menopause had occurred at age forty-six. She dated the onset of her rheumatoid arthritis to age forty-five. Since that time she had had mild but persistent multiple joint involvement but usually was able to perform her work as a factory machine operator. She had never received gold or corticosteroid treatment. For about six months before admission to the hospital in June 1956, she had noted weakness and mild pain in the knees. For a month prior to admission she was unable to walk and numbness developed over the dorsa of both feet without parathesias.

On neurologic examination the lower limbs were weak, more so on the left side. There was foot drop bilaterally, and sensation was diminished over the dorsa of both feet. The left ankle jerk was absent. Spinal fluid examination was within normal limits.

Glycosuria was detected on admission and a glucose tolerance test was in the diabetic range. A biopsy of the gastrocnemius muscle was performed and extensive arteritis with a few foci of necrosis was seen. During the next several months she gradually recovered sensation and muscle strength in the lower part of her legs. In the latter half of 1956, episcleritis developed. By January 1957, the neurologic defects had almost completely disappeared.

Comments: This patient with advanced rheumatoid arthritis had never received gold or corticosteroid drugs. Diabetes was discovered at the time of admission to the hospital. The peripheral neuritis was attributed to the inflammatory involvement of small arteries which was demonstrated by biopsy. Healing of both vessel and nerve lesions is presumed to have occurred since she recovered completely from the peripheral neuritis.

CASE 6. This Negro housewife was seen in July 1955 at the age of forty-five. In 1954, multiple peripheral joints became swollen and painful. Cortisone was prescribed from January to April 1955 in doses of 160 mg. daily, then prednisone in an unknown amount was substituted and continued until she was seen at Bellevue. Her eyes had always been considered prominent but investigation revealed thyroid function to be normal.

In May 1955 mild episcleritis developed. In August the episcleritis became severe so that she was admitted to the Ophthalmological Service of Bellevue Hospital where it was necessary to raise the prednisone dosage from 20 to 60 mg. a day to control this manifestation. Afterwards the dose was reduced to 20 mg. In February 1956, she noted the sudden onset of left foot drop with an area of anesthesia over the dorsum of the left foot. A biopsy specimen of the left anterior tibial muscle revealed a small area within a single artery involved by necrotizing arteritis. Since she felt well in other respects, it was decided to continue the corticosteroid medication unchanged. During the next several months the foot drop completely disappeared and by early 1957 no further numbness of the leg was detected. In June 1956 she was admitted for hysterectomy because of excessive vaginal bleeding. She went into shock twelve hours postoperatively but responded to the intravenous administration of additional corticosteroids. The operative specimen showed no evidence of arteritis.

Comment: While this patient was being treated with corticosteroids peripheral neuritis developed, and necrotizing arteritis was found on biopsy. Although corticosteroid therapy was continued, the arteritis presumably healed because all evidence of the nerve lesion dis-

appeared subsequently. She continues well at the present time.

CASE 7. This white housewife was first seen in January 1954 at the age of twenty-seven. During her first pregnancy at age nineteen she had swollen feet and was told she had elevated blood pressure and albuminuria. Two weeks postpartum, she noted that, for a few minutes, she could not move her left arm or left leg. This resolved spontaneously. A second pregnancy at age twenty-four was uneventful.

Rheumatoid arthritis began at age twenty-two with involvement of multiple peripheral joints. The disease was progressive except for a mild remission during the second pregnancy. In 1953, at age twenty-six, cortisone therapy was begun at a dosage level of 100 mg. daily. It was later reduced to 50 mg. a day. Predisone was substituted in March 1955 at a level of 15 mg. a day. Her disease continued to be active while she received these medications and she had to limit her duties as a housewife. Because of this persistent rheumatoid activity, a course of gold treatment was begun as additional therapy in October 1956; 5 mg. was given as the first dose and albuminuria appeared. Gold therapy was continued for several injections and then stopped because of the persistence of albuminuria.

The patient was admitted to the hospital for evaluation of her renal status. On admission the patient recalled that for the past month she had had a tingling sensation over the left thumb and index finger and the back of the left hand and forearm which lasted several weeks. There was no associated muscle weakness. For the few weeks previous to admission the right great toe had been numb, with absence of touch and pain sensation, but motion was normal. A diagnosis of peripheral neuritis was made and a biopsy specimen of the right gastrocnemius muscle was secured. A single small focus of apparently healing necrotizing arteritis was found; in addition an arteriole showed inflammation without necrosis. Results of renal function tests were normal. The reaction to a Congo red test was normal and a gingival biopsy specimen revealed no evidence of amyloid deposition. Prednisone therapy has been continued at doses of about 15 mg. daily; neurologic symptoms have disappeared.

Comment: The symptoms of peripheral neuritis were mild and transient in this patient. Because of the neuritis, a muscle biopsy specimen was obtained and very mild necrotizing arteritis was found.

CASE 8. This fifty-six year old white woman was first seen in 1951. The onset of her rheumatoid arthritis occurred in 1945 with involvement of almost all peripheral joints. Cortisone therapy was begun in 1951 and continued at levels of 50 to 75 mg. daily until

the spring of 1955. She had had symptoms that were attributed to peptic ulcer in 1925.

In January 1953, ulcer symptoms developed again and she began to note numbness of the fingers of both hands. The numbness persisted for about one year. A biopsy specimen of subcutaneous fibro-adipose tissue was obtained in May 1953. It revealed fibrosis of the intima and recanalization of the lumen of small arteries suggestive of healed endarteritis. An episode of melena occurred in September 1954. In April 1955, the corticosteroid therapy was discontinued because of gastrointestinal symptoms. At this time a duodenal ulcer was demonstrated by x-ray, whereas previous films in 1952, 1953 and 1954 were normal. Her subsequent course to date has been marked by minimal evidence of activity of her rheumatoid arthritis.

Comment: Eight years after the onset of her rheumatoid arthritis evidence was found in this patient of arteritis that had healed sometime before the biopsy was performed. Several months before the biopsy peripheral neuritis (finger-tip numbness) had developed.

Case 9. In this white man rheumatoid disease began at the age of thirty-four in 1946; it was initiated by an attack of acute pericarditis. Within a few months, multiple joint and muscle pains developed, but there was little objective evidence of joint disease. Within a short time numerous subcutaneous nodules appeared. He was admitted to Bellevue Hospital in December 1948 while his disease was still active. A biopsy specimen of gastrocnemius muscle revealed non-necrotizing arteritis (M-182, [71]). On biopsy of a subcutaneous nodule the characteristic rheumatoid granuloma was found.

In January 1949, the patient was transferred to Goldwater Memorial Hospital, New York, for chronic care; he remained there for one year. During this interval he had gradual return of all function and went into complete remission. Shortly after entering that hospital he noted ptosis of the eyelids, predominantly on the right side. The ptosis was unrelated to the time of day or the patient's activity. It persisted for several weeks. Other neurologic functions were normal.

When seen in January 1957 he appeared in normal health and complete examination disclosed no abnormality except for diminished pulsations in the left leg below the femoral artery. A family history of arteriosclerosis in several siblings was recorded.

Comment: In this patient rheumatoid arthritis developed at the age of thirty-four and continued to be active until age thirty-eight. It was characterized by features suggesting dissemination. For the past six years his disease has been in complete remission. It is of interest that shortly after non-necrotizing arteritis was found

in a biopsy specimen of gastrocnemius muscle, the patient experienced temporary ptosis of both eyelids. It is possible that this muscular weakness was due to arteritis of the nerves supplying the Levator palpebrae. No corticosteroids were ever administered.

Case 10. This white widowed former saleswoman had rheumatoid arthritis which began in 1942 when she was forty-four years old. A review of her old records disclosed a possible episode of peripheral neuritis in 1944 involving the right forearm. From 1946 until the present she had had numerous episodes of conjunctivitis of both eyes. In 1949 keratitis sicca was noted, and later painful parotid swelling. A diagnosis of Sjögren's syndrome was then made. A biopsy of the right gastrocnemius muscle was performed in March 1948 revealing non-necrotizing arteritis (M-62, [71]). The patient had received gold in the past but had not been given corticosteroids up to the time of biopsy. Later (December 1953) she received hydrocortisone for three weeks because of low grade, chronic joint symptoms.

In the spring of 1954 she noted increasing pain and numbness of the left hand along the ulnar border. Neuritis of the left ulnar nerve was diagnosed; it was considered to be secondary to arthritic changes at the elbow impinging on the adjacent nerve. For this reason surgical transplantation of the nerve was performed in April 1954. No biopsy specimens were taken. In the next year or so the symptoms of the neuritis gradually cleared.

When seen in 1957 she had residua of advanced rheumatoid arthritis, but with little or no activity. Results of the agglutination and inhibition tests for the rheumatoid factor were negative. She was able to perform limited household duties. She had left the hospital the year previously, after spending over ten years as an inpatient. Examination in 1957 revealed no neurologic disorder.

Comment: This patient has had rheumatoid arthritis for the past fifteen years. She had not received steroids prior to the demonstration of non-necrotizing arteritis by muscle biopsy in 1948. A syndrome suggestive of peripheral neuritis occurred in 1944 and definite ulnar neuritis developed in 1954. That this ulnar neuritis wss due to mechanical injury to the nerve is possible, but it should be noted that, at operation, no focal inflammatory lesion was described in the nerve as it passed the elbow joint. The patient was free of symptoms of neuritis when the biopsy was performed and for five years thereafter. In addition to the classic features of rheumatoid arthritis, this patient had the findings of Sjögren's syndrome.

Arteritis and Systemic Disease Other than Peripheral Neuritis, (Cases 11 to 13). In three patients in whom peripheral neuritis did not develop, evidence of systemic involvement thought to have been due to arteritis occurred in other organs. Biopsy was carried out to determine whether vascular inflammatory disease existed; arteritis was found.

Case 11. This white housewife, born in Colombia, South America, was first seen in January 1956 when she was fifty-six years old. Her rheumatoid arthritis began at the age of twenty-five. It gradually involved almost all the peripheral joints. Nevertheless, she was ambulatory until 1949. In 1950 she received gold therapy. Between 1950 and 1954 she received corticosteroid medication but the dosage and length of treatment are not known. In 1954 episcleritis

developed.

The patient was admitted to Bellevue Hospital in January 1956 for surgical correction of rheumatoid deformities. On March 12, 1956, she was found to have abdominal rebound tenderness and distention. An obstructing lesion of the sigmoid was considered and an exploratory laparotomy was undertaken. Inspection of the abdominal organs, however, failed to reveal any lesion. The patient recovered after a febrile postoperative course that was complicated by pneumonia in the lower right lung. Pleural friction rubs were heard over both lung fields. She had been given prednisone from January until April 1956, during the time of her reconstructive surgery. The administration of this drug was discontinued after April. One year later, in March 1957, she had fever with temperatures of 103° to 104°r. and there was a marked increase in the size of the cardiac shadow on the roentgenogram. A pericardial friction rub was heard, and the electrocardiogram showed a decrease in the amplitude of the QRS complexes. An L.E. cell preparation was positive.

Because of the systemic nature of this patient's illness, a biopsy specimen of gastrocnemius muscle was obtained in 1957. It revealed necrotizing arteritis; non-necrotizing inflammation of venules and capillaries was seen also. No further complications have

occurred.

Comment: This patient has had an unusually long and severe form of deforming rheumatoid arthritis. She recalled no neurologic symptoms. In the last eighteen months, however, she has had symptoms of systemic illness accompanied by a positive L.E. cell test. Muscle biopsy revealed necrotizing arteritis. The findings may be interpreted as disseminated rheumatoid disease with a "false-positive" L.E. test or as an example of systemic lupus erythematosus super-

imposed upon pre-existing classic rheumatoid arthritis. In either case some of the systemic features of this patient's disease are probably related to vascular inflammation.

CASE 12. This male practical nurse was seen in 1953, at the age of fifty-seven. He had noted symptoms of rheumatoid arthritis with involvement of multiple peripheral joints in 1947. Gold treatment was given in 1948. When seen in 1953 he had gynecomastia bilaterally, hypertension, an emphysematous chest and a murmur suggestive of mitral stenosis. On later occasions this murmur could not be heard. There was clubbing of the fingers and a diffuse increase of interstitial lung markings on chest films.

Hydrocortisone therapy was begun in February 1953 and continued at levels of 50 to 60 mg. daily to the time of death. A biopsy specimen of gastrocnemius muscle obtained in July 1953 revealed arteritis and arteriolitis; there was no evidence of necrosis. In August cardiac decompensation developed which improved with the administration of mercurial diuretics and digitalization. In January 1954 the patient was found to have hyperreflexia and a Babinski sign on the right side. In July 1954 he became acutely ill and apparently was either comatose or paralyzed for several days at home. The patient was confused about his symptoms.

In an attempt to reduce the amount of cortisone required he was given 500 mg. of chloroquine a day for three months in the fall of 1954 but no beneficial effect was noted. The congestive failure continued to progress and he was admitted to the hospital in May 1955. Sterile, cloudy fluid was aspirated from the left side of his chest. Bronchoscopy disclosed no lesions. He had a low grade fever throughout with temperatures that rose to 104° to 106°F. for the last three days of life. Permission for autopsy could not be obtained.

Comment: This patient presented evidence of systemic but undiagnosed disease involving the heart and lungs. He also had signs of central nervous system disease but no peripheral neuritis. Muscle biopsy revealed non-necrotizing arteritis six years after onset of rheumatoid arthritis and five months after hydrocortisone therapy had been begun. Although cerebral arteriosclerosis may have caused his neurologic symptoms, the possibility of arteritis of these vessels cannot be excluded.

Case 13. The patient, a white carpenter, noted the onset of arthritis involving multiple peripheral joints in 1945 at the age of fifty-two. He had "pneumonia" at age twenty. A lary ngeal polyp was removed at age forty-nine following a sudden episode of respiratory distress. Chest roentgenograms available since 1950 have revealed a constant "coin" lesion in

the fourth left interspace. In 1950 an area of paresthesia was noted over the lateral aspect of the right thigh from the hip to the knee. In 1951 the patient received a course of gold without effect. Cortisone therapy was begun in June 1951 and he was able to resume work. Corticosteroids in daily dosage of about 75 mg, were given until his death.

In January 1954 an electrocardiogram disclosed right bundle branch block. The patient had been experiencing chest pain which encircled the thorax and bore no relation to effort. A rough systolic and early diastolic sound was heard that lasted several weeks and was considered to be a pericardial friction rub. A gastrocnemius muscle biopsy in March 1954 revealed a single focus of non-necrotizing arteritis. (Fig. 6.) In June 1955 he first showed glycosuria and a glucose tolerance test was diabetic in type. The dosage of corticosteroids was reduced. In July 1955 he experienced an episode of dizziness which lasted several days. He was thought to have had a cerebral vascular accident but no neurologic signs were found. The spinal fluid was normal except for an elevated protein (76 mg. per cent). In January 1957 he fell and was unconscious for a few minutes. He was taken to a local hospital where he died. At autopsy, vascular occlusion causing cerebral infarction was noted. A hamartoma in the lung was found to explain the "coin" lesion seen radiologically. No arteritis was found, but muscle was not examined.

Comment: This patient had had rheumatoid arthritis for nine years and had been receiving corticosteroids for three years when a biospy disclosed non-necrotizing arteritis. He died from cerebral vascular complications of generalized arteriosclerosis. Generalized disease related to rheumatoid arthritis was minimal but included pericarditis and an episode of probable peripheral neuritis.

Arteritis Without Obvious Systemic Symptoms (Cases 14 to 17). Four patients were found to have arteritis on biopsy in the absence of suggestive clinical symptoms. The patients were taken at random; two being part of the series of patients originally reported by Sokoloff, Wilens and Bunim [71].

CASE 14. This man was first seen in 1952 when he was fifty-nine years old. His arthritis began in 1947 and involved many peripheral joints. Except for one brief remission, his disease activity was persistent although moderate. He received gold in 1948.

For several years he had noted dyspnea on effort for which digitalis had been prescribed. In 1952 a chest film disclosed segmental collapse of the lower lobe of the right lung. Signs of pulmonary emphysema were present. A biopsy specimen from the gastro-

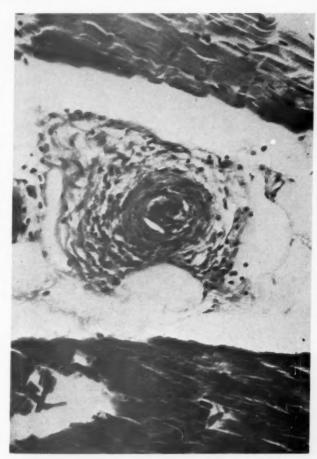


Fig. 6. Case 13. Non-necrotizing arteritis in a small artery of gastrocnemius muscle; hematoxylin and eosin stain.

cnemius muscle in February 1952 disclosed arteritis with a minimal area of necrosis. The patient, who had not previously received corticosteroid therapy, was started on cortisone after the biopsy. However, this was discontinued in May 1952 because of perforation of a duodenal ulcer. The perforation was closed surgically. The patient was last heard from in 1953, at which time he wrote that he felt improved.

Comment: This patient with rheumatoid arthritis had arteritis with minimal necrosis on biopsy prior to the administration of cortisone. No systemic symptoms were apparent during the period of observation.

Case 15. An unmarried white tailor was first seen in 1952 at the age of sixty-four because of multiple joint pains in the previous six months. He had contracted gonorrhea in 1937. On examination in 1952 he was found to have few objective joint changes. In the next six months he lost 15 pounds in weight. Phenylbutazone was given for three months, with little effect. A course of gold injections was begun in January 1954. In February, objective swelling of numerous joints was recorded and 62.5 mg. cortisone

TABLE IV
CLINICAL FEATURES OF FOURTEEN PATIENTS WITH RHEUMATOID ARTHRITIS
WHO HAD NO VASCULAR LESIONS ON BIOPSY

Case No.	Sex	Age at Onset of Rheumatoid Arthritis (yr.)	Stage of Disease*	Sub- cutaneous Nodules	Epi- scleritis	Hyper- tension	Duration Arthritis Before Biopsy (yr.)	Steroid Therapy Before Biopsy (mo.)	Present Status
18	F	48	3	+	0	0	7	48	Living
19	M	52	3	Ó	0	+	15	1	Living
20	F	39	4	+	0	+	28	19	Living
21	F	30	2	0	0	0	8	36	Living
22	F	35	3	0	0	+	4	6	Living
23	F	44	3	+	+	0	8	54	Died
24	F	47	3	+	0	+	5	7	Died
25	M	56	3	0	0	+	6	38	Living
26	M	5	2 3	0	0	±	6	33	Living
27	F	41	3	0	0	+	12 and 13	8 and 20†	Living
28	F	27	2	0	0	0	6 mo.	0	Living
29	F	54	3	0	0	0	3	In past‡	Living
30	F	22	4	+	0	0	31	0	Living
31	F	8	2	0	0	0	8	In past §	Living

Note: + = symptom present; 0 = symptom absent; ± = symptom variable, often absent.

* Stage of rheumatoid arthritis according to classification of the American Rheumatism Association [72].

† Two separate biopsies performed.

Corticosteroids stopped one year before.

§ One patient (Case 31) received corticosteroids for eighteen months in second and third year of illness and previously reported on by Bunim, Kaltman and McEwen [8].

daily was added to the gold treatment in March to control the acute symptoms. During April he noted ulcer symptoms and a prepyloric ulcer was evident on roentgenograms. After 1,200 mg. of gold had been administered with little effect, therapy with this drug was discontinued in May. At the same time, because of the ulcer, the administration of cortisone was stopped for two months but had to be resumed in the same dosage because of the severity of the arthritis. In April 1955 prednisone was substituted for cortisone and continued at levels of 15 to 25 mg. daily to the present. His weight was stabilized until 1956 when it again began to fall; he lost 20 pounds during the subsequent year. A biopsy specimen of gastrocnemius muscle was obtained in March 1957 and necrotizing arteritis was found.

Comment: In this patient, rheumatoid arthritis began at the age of sixty-four with a continually active course since that time. Little deformity has occurred. He has received corticosteroids continuously for over three and a half years except for a brief interval, early in the course of therapy, when a peptic ulcer developed. No neurologic abnormalities have been ob-

served, but necrotizing arteritis was found on muscle biopsy.

Case 16. This white, divorced factory worker had tuberculosis at the age of fourteen and pleurisy at age twenty-seven. At age forty-two, in 1936, he noted the sudden onset of severe pain in the peripheral joints which lasted for several months. These recurred in 1947 when he was fifty-three years old. At this time a biopsy specimen of the quadriceps muscle revealed non-necrotizing arteritis (M-16, [71]). Gold treatment was then begun in small dosage. In 1949 the patient returned to his native country, Switzerland. Follow-up information was made available by Dr. D. Speiger of the Universitäts-Rheumaklinik of Kantonspital, Zürich, Switzerland, through the courtesy of Professor Böni. The patient had been able to resume light factory work despite several flare-ups of his arthritis in 1950, 1952 and 1955. In 1955 he received two courses of hydrocortisone for ten days each. The patient has not had any neurologic symptoms. His disease is considered to be mildly active at the present time.

Comment: At present the patient is sixty-three years old; he has had rheumatoid arthritis since age fifty-three. A muscle biopsy early in the

course of his disease, at age fifty-three, revealed definite although minimal non-necrotizing arteritis. He has not shown any unusual clinical features.

Case 17. In this white woman, sixty-three years of age, pain and swelling of the left knee developed in 1948. Other peripheral joints were soon involved. Biopsy of the gastrocnemius muscle, six months after onset of the rheumatoid arthritis, disclosed inflammatory changes in two small arteries without necrosis (M-175, [71]). The rheumatoid arthritis was progressive during the next several years. She was confined to a nursing home during this time. No corticosteroids were administered.

In July 1955 a high fever developed suddenly and she was transferred to a local hospital. She arrived in a semicomatose state with a temperature of 106.3°F. She was cyanotic and the abdomen was distended. Blood pressure was not measurable and she died within two hours. No autopsy was performed.

Comment: This patient with rheumatoid arthritis was found to have non-necrotizing arteritis six months after the onset of her disease. The cause of the terminal acute illness is not known. Although the information received from the hospital at which she died is not complete, no mention was made of a neurologic lesion.

No Arteritis Detected on Biopsy (Cases 18 to 31). There were fourteen patients in whom no vascular inflammation could be domonstrated after careful examination of a biopsy specimen. Of these, six (Cases 18 to 23) presented symptoms that were suggestive of disseminated visceral disease and therefore were biopsied. The remaining eight (Cases 24 to 31) were taken at random and did not show unusual manifestations of rheumatoid arthritis. Because of the high index of suspicion that attaches to peripheral neuritis as a symptom of arteritis, the findings in the three patients with neuritis (Cases 18 to 20) are given in more detail; data for the entire group are recorded in Tables IV and V.

CASE 18. The patient, a white, unmarried secretary, was first seen in April 1956 at the age of fifty-six. She had been aware of an asymptomatic goiter for over ten years. Menopause at age fifty-two was uneventful. In 1948 an acute illness developed which was diagnosed as bursitis in one shoulder; it subsided in a few weeks. In 1950 the pain recurred in both shoulders and shortly thereafter multiple peripheral joints became involved. Cortisone therapy was begun in 1951 and continued at levels of 50 and then 100 mg. daily; by 1953 her disease had become so advanced that she had difficulty in continuing on her job.

Table v
Laboratory features of fourteen patients with
RHEUMATOID ARTHRITIS WHO HAD NO VASCULAR
LESIONS ON BIOPSY

Case No.	Rheumatoid Factor (Euglobulin Agglutination)*	L.E. Factor	Hemoglobin (<12 gm. %)	Protein- uria
18	28	0	+	±
19	56	0	+	0
20	896	0	++	0
21	112	0	+	0
22	224	0	0	0
23 †	28	0	+	+
24	224	N.P.	+	+ + 0
25‡	56	0	+	0
26	28	0	+	0
27	224	+	+ 1	±
28	14	+ 0	0	0
29	N.P.	0	+	0
30	14	0	0	0
31	14	0	0	0

Note: + = test positive; 0 = test negative; \pm = test variable, often negative; N.P. = test not performed.

* Highest titer of each patient expressed as the reciprocal of the greatest dilution that caused agglutination.

† Amyloid disease noted in kidneys and other organs at postmortem.

‡ Anemia due primarily to blood loss from gastrointestinal tract.

A chest roentgenogram at that time revealed a dense triangular shadow in the area of the middle lobe of the right lung. Numerous studies, including bronchoscopy, failed to disclose the cause of this lesion. On May 11, 1955, she noted fever and tingling and weakness in the lower part of her left leg as a result of which she fell and suffered a fracture of the left internal malleolus. She was admitted to Bellevue Hospital on May 13, 1955. In addition to the fracture and previous findings she had leukocytosis at this time and temperatures of 101° to 102°F. that continued for about a month. About four to six weeks after admission similar simptoms appeared in the right foot.

Biopsy was not performed until several months later and a specimen was taken from the right deltoid muscle. In this specimen no evidence of vascular reaction was seen. Because of non-union of the fracture corticosteroid therapy was gradually tapered in the latter half of 1955 and she has been maintained without these drugs since, except for a brief period in 1957. The bilateral foot drop with decreased sensation to touch and pain over both feet has remained unchanged.

Comment: In this patient with advanced rheumatoid arthritis typical symptoms of periph-

eral neuritis developed after several years of corticosteroid therapy. The biopsy specimen did not reveal arteritis. However, it was obtained about four months after the onset of symptoms and from a muscle distant from the site of neurologic involvement. It is thought that a vascular lesion had developed in this patient but no histologic proof of this was obtained.

Case 19. In this white unskilled laborer rheumatoid arthritis developed in multiple joints in 1941, at age fifty-two. He was treated with salicylates and a long course of gold. He received corticosteroids for only a few weeks in 1953. At age twenty-five he was treated for gonorrhea and in 1943, at age fifty-four, was admitted to Bellevue Hospital for acute epididymitis. His arthritis continued as a mild disease which did not interfere with his working.

In September 1951 he was readmitted to the hospital because of melena. Extensive clinical studies did not reveal any source for the bleeding. In 1952 and 1953 peripheral vascular disease was noted in the feet and diagnoses of obliterating arteriosclerosis and varicose veins were made. In January 1954 a pleural friction rub was heard in the right side of the chest. Roentgenograms disclosed an infiltrate in the lungs and acid-fast bacilli were found in the sputum. He received a course of streptomycin and para-aminosalicylic acid.

On August 30, 1956, he awoke to find that he could not extend the fourth and fifth fingers of the right hand. A patch of anesthesia was noted on the dorsal and ulnar side of the hand. Peripheral neuritis was diagnosed and a biopsy specimen was obtained from the extensor muscles of the right forearm. Cellular infiltrations were noted around one venule but no evidence of arteritis was found. During the next several months he gradually recovered function of the involved hand.

In January 1957 gastrointestinal hemorrhage occurred but again no source for the bleeding could be found. In the spring of 1957 gangrene of the big toe of the right foot developed following a paronychia. The gangrene progressed so that in June 1957 a midthigh amputation was performed. Unfortunately no tissue studies were made.

Comment: This patient had had rheumatoid arthritis for seventeen years, with only slight deformity and little functional impairment. He received corticosteroids for only three weeks in the twelfth year of the disease. Typical peripheral neuritis developed in the fifteenth year of his arthritis. Despite careful examination of an adequate biopsy specimen, arteritis was not found.

Case 20. Arthritis of the wrist and hands developed in this white widowed housewife in 1925 when

she was thirty-nine years old; it lasted for several months. In 1943 the arthritis returned to involve almost all peripheral joints. No subsequent remission has occurred. A course of gold injections was administered in 1948, without success. Subcutaneous nodules have been present over the elbows since 1945.

When first seen in 1951, in addition to these findings, a harsh systolic apical murmur was heard. Serum globulin was elevated to 5.1 gm. per cent. Treatment with cortisone was begun in December 1951 and continued to February 1955 at dosage levels of 62.5 to 87.5 mg. daily. Prednisone was then substituted at levels of 10 mg. daily. A biopsy specimen of gastrocnemius muscle was obtained on July 16, 1953. No arteritis was seen. In January 1954 she noted intermittent numbness of the right first digit and had difficulty in winding a watch. During the next six to nine months she experienced further numbness of the distal parts of several fingers. Since this time no further neurologic symptoms have appeared.

Comment: This patient was suspected of having arteritis when the peripheral neuritis occurred. Unfortunately, no biopsy specimen was procured at that time, although one obtained six months before had not shown any vascular inflammation.

Three other patients experienced symptoms of generalized disease. In one (Case 21) there was gross tremor of the extremities, muscle weakness and incoordination. Spinal fluid examination, cerebral arteriograms and ventriculography did not disclose any abnormality. In another patient (Case 22) who had schizophrenia and recovered sufficiently to leave a mental institution, an unexplained episode of papilledema developed and lasted a few weeks. The third patient (Case 23) was noted at postmortem examination to have amyloidosis of the abdominal viscera, including the kidney. She had had persistent proteinuria for many years. Biopsy was performed on these three patients but no arteritis was found.

Of the remaining eight patients (Cases 24 to 31) who likewise did not show arteritis on biopsy no features of their medical histories were thought to suggest extra-articular rheumatoid disease. All were taken at random from the clinic. The cause of death in one (Case 24) was not known since the patient died in another hospital in February 1957 about a year following her last visit to our clinic.

ANALYSIS OF FINDINGS

Comparison of Patients with Arteritis and Those Without Arteritis on Biopsy. An analysis of various

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clinical and laboratory features of the seventeen patients with and the fourteen patients without arteritis demonstrated by biopsy has been made. (Table vi.) The findings direct attention toward possible differences between the two groups.

Both groups were roughly comparable in some respects. There was the expected higher incidence in females. The mean age of onset of rheumatoid arthritis was ten years higher in the group with arteritis (forty-six years compared to thirty-six years) although the duration of the disease until biopsy (nine and ten years, respectively) and the incidence of advanced deformity and structural change (stage of disease) were about the same. The percentage treated with corticosteroids and the average length of this treatment (twenty-six months in each group) were not greatly different. So, too, was the high incidence of positive test results for the rheumatoid factor and anemia, and the low incidence of hypertension and proteinuria. There was a slight tendency for patients with arteritis to have higher titers of the rheumatoid factor. (Tables III and v.) In summary, the average patient of either group had long-standing rheumatoid arthritis with moderate to severe bone erosions and mild to moderate anemia, and in most cases had been maintained on corticosteroids.

Several features tended to be more commonly seen in the group who had vascular inflammation on biopsy. Subcutaneous nodules were found in almost all the patients with vascular inflammation but only in slightly more than a third of those without arteritis. Peripheral neuritis, pericarditis diagnosed clinically, episcleritis and a positive L.E. cell reaction were noted in from 24 to 59 per cent of those with arteritis but were seen only rarely in those without arteritis. Indeed, no evidence of any unusual extra-articular disease was found in almost three-fifths of the group without arteritis, whereas less than a quarter of the group with arteritis had a similar lack of systemic findings. Thus there seems to be an association between symptoms of systemic disease and the presence of arteritis. In particular, certain symptoms such as peripheral neuritis, pericarditis, episcleritis and subcutaneous nodules, when present, are suggestive indications that the patient is a candidate for detectible vascular inflammatory disease. The L.E. cell phenomenon and perhaps higher titers of rheumatoid factor may likewise be helpful in the evaluation of arteritis.

Table VI
COMPARISON OF VARIOUS CLINICAL AND LABORATORY
FEATURES IN THIRTY-ONE BIOPSIED PATIENTS
WITH AND WITHOUT ARTERITIS

	W	tients vith tis (17)*	Patients Without Arteritis (14)		
Clinical or Laboratory Finding	No. (Per cent) with Find- ing	Total No. Ob- served	No. (Per cent) with Find- ing	Total No. Ob- served	
Male patient	7 (41)	17	3 (22)	14	
Age onset of rheumatoid arthritis forty years or more	13 (77)	17	7 (50)	14	
Duration arthritis before biopsy five	13(11)	1/	1 (30)	14	
or more years	13 (77)	17	11 (79)	14	
Duration steroid therapy before bi-	22 (1.1)	**	()		
opsy twelve or more months	8 (73)	11	9 (75)	12	
Patients on steroid therapy before					
biopsy	11 (65)	17	12 (84)	14	
Patients in stage 3-4†	13 (77)	17	10 (71)	14	
Subcutaneous nodules	14 (82)	17	5 (36)	14	
Episcleritis	5 (29)	17	1 (7)	14	
Hypertension	6 (35)	17	7 (50)	14	
Clinical pericarditis	5 (29)	17	0(0)	14	
Peripheral neuritis	10 (59)	17	3 (21)	14	
Other systemic findings	3 (18)	17	3 (21)	14	
No systemic findings	4 (24)	17	8 (57)	14	
Rheumatoid factor	15 (94)	16	13 (100)	13	
L.E. factor	4 (31)	13	1 (8)	13	
Anemia (less than 12 gm.)	11 (65)	17	10 (71)	14	
Proteinuria	4 (24)	17	4 (29)	14	

* Numbers of patients

† Stage of rheumatoid arthritis according to classification of the American Rheumatism Association [72].

Comparison of Patients with Necrotizing and Those with Non-necrotizing Arteritis. Classifications of arteritis using histologic criteria have customarily distinguished between necrotizing and nonnecrotizing arteritis. In this report necrosis was considered to be present when markedly eosinophilic "fibrinoid" and nuclear fragments were seen within the arterial wall, even if in only a small segment of one artery. In a few instances, previously necrotic lesions that had healed were deduced from the presence of scars and capillaries in the vessel wall. Arteritis without necrosis was diagnosed when a cellular inflammatory reaction was noted primarily within the arterial wall without other foci of inflammation in immediately adjacent tissue. Whether the occurrence of necrosis represents a qualitative or a quantitative difference in these two types of lesions is not known.

The findings in the seventeen patients with arteritis were analyzed to determine whether any clinical or laboratory abnormalities were more frequently associated with the necrotizing

TABLE VII

COMPARISON OF VARIOUS CLINICAL AND LABORATORY FEATURES IN SEVENTEEN BIOPSIED PATIENTS WITH NECROTIZING AND NON-NECROTIZING ARTERITIS

	Necr	tients with otizing tis (11)*	Patients with Non-necrotiz ing Arteritis (6) *		
Clinical or Laboratory Finding	No. (Per cent) with Find- ing	Total No. Ob- served	No. (Per cent) with Find- ing	Total No. Ob- served	
Male patients	3 (27)	11	4 (67)	6	
Age onset of rheumatoid arthritis forty years or more	8 (73)	11	5 (83)	6	
Duration arthritis before biopsy five	0 (13)	**	3 (03)	0	
or more years	9 (82)	11	4 (67)	6	
Duration steroid therapy before bi-	1 , , , ,	-	,,,,		
opsy twelve or more months	7 (78)	9	1 (50)	2	
Patients on steroid therapy before					
biopsy	9 (82)	11	2 (33)	6	
Patients in stage 3-4†	9 (82)	11	4 (67)	6	
Subcutaneous nodules	9 (82)	11	5 (83)	6	
Episcleritis		11	0 (0)	6	
Hypertension	3 (27)	11	3 (50)	6	
Clinical pericarditis	3 (27)	11	2 (33)	6	
Peripheral neuritis	8 (73)	11	2 (33)	6	
Other systemic findings	1 (9)	11	2 (33)	6	
No systemic findings	2 (18)	11	2 (33)	6	
Rheumatoid factor	11 (100)	11	4 (80)	5	
L.E. factor	4 (40)	10	0 (0)	3	
Anemia (less than 12 gm.)	8 (73)	9	3 (50)	6	
Proteinuria	2 (22)	9	1 (17)	6	

* Number of patients.

†Stage of rheumatoid arthritis according to classification of the American Rheumatism Association [72].

than with the non-necrotizing variety. (Table VII.) Such might be expected because narrowing, sometimes to the point of virtual occlusion of the involved vessel, was often noted in necrotizing and not in non-necrotizing arteritis. As a consequence, signs of ischemia might develop in tissue supplied by the artery.

For most of the factors considered, there was little or no significant difference either between each of the two groups with arteritis or, in fact, between these two groups and the group with a negative biopsy. These included the age of onset and duration of rheumatoid arthritis and the duration but not the incidence of steroid therapy before biopsy, the marked degree of joint destruction and the incidence of hypertension, positive test results for the rheumatoid factor, anemia and proteinuria. Subcutaneous nodules, however, were present in almost all, and pericarditis in a lesser but equal number of patients with both types of arteritis whereas they were much less common in the group without arteritis on biopsy (vide supra).

Some features did occur more frequently with necrotizing arteritis. These features included peripheral neuritis, episcleritis and the presence of L.E. cells. Peripheral neuritis was present in almost three-quarters of the group with necrotizing arteritis and only one-third of the group with non-necrotizing arteritis. The L.E. phenomenon and episcleritis were found in almost half of the group with necrotizing arteritis but both were strikingly absent in the group with non-necrotizing arteritis. Possibly these clinical and laboratory findings are associated with the presence of necrosis and occlusion of the artery rather than with inflammation alone. On the other hand, subcutaneous nodules and pericarditis, which were present in both groups with arteritis but not in the group with a negative biopsy, may be related to inflammation of the arterial wall rather than to vascular necrosis and occlusion.

The Relationship of Corticosteroid Treatment and Arteritis. The large majority of our patients had been treated with corticosteroids as well as numerous other medications. Corticosteroids were administered to almost all patients (twelve of fourteen) with a negative biopsy as well as to an almost equal number of patients (eleven of seventeen) with arteritis. (Table vi.) Of the eleven who had arteritis and had received prior treatment with corticosteroids, nine had necrotizing and only two had non-necrotizing arteritis whereas of the six patients with arteritis who had never received these drugs two had necrotizing and four non-necrotizing arteritis. (Table vii.) These data suggest a possible association between necrosis in the vascular lesion and the prior use of these drugs. However, it is obvious that necrosis of the arterial wall sometimes does occur without exogenous corticoids (two of eleven patients) and also that corticosteroids were just as frequently employed in the group with a negative biopsy. It does not appear possible from our data to draw firm conclusions; however, the findings suggest that corticosteroid therapy, if indeed it plays any role in the development of arteritis in patients with rheumatoid arthritis, cannot be the only factor since these lesions occur in the absence of such therapy.

Peripheral Neuritis as a Diagnostic Sign of Arteritis. Of the various features that have been shown to appear more frequently in patients with arteritis the development of peripheral neuritis has proved most useful as a diagnostic

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sign. It occurred in 59 per cent of the total group with arteritis and in 73 per cent of the group with necrotizing arteritis, more often than other findings suggestive of systemic disease. Its presence is easily detected if one takes a careful history for sensory changes in the extremities and distinguishes between true paralysis and apparent inability to move a limb because of painful arthritis. In most instances the patient is aware of the new symptom.

During the course of their rheumatoid arthritis sixteen patients were observed to have peripheral neuritis for which no known toxic, infectious or metabolic cause was apparent. Diabetes mellitus was present in three patients (Cases 1, 5 and 13) but as far as is known inflammatory disease of small arteries has not been implicated in the neuritis of this disease. Biopsy was performed in thirteen of the sixteen and was positive in ten instances, eight having necrotizing and two non-necrotizing arteritis. Three patients (Cases 32 to 34) were not biopsied but are included to amplify the clinical picture. Two of them had subcutaneous nodules and one of these two (Case 32) had an enlarged spleen and had had episodes that were compatible with the diagnosis of pericarditis.

In seven positive biopsies (Cases 1 to 7), muscle tissue was obtained within a few weeks after the onset of neuritis and often from the muscle supplied by the involved nerve. Active necrotizing arteritis was present. In the eighth patient (Case 8), biopsied several months after neuritis developed, healing of the necrotic vascular lesion had already taken place. Further, in two of these patients (Cases 2 and 3), biopsied twice, the earlier negative biopsy had been obtained when neurititis was absent. In both of the patients with non-necrotizing arteritis in whom symptoms of neuritis developed (Cases 9 and 10) the biopsy had been performed before neuritis appeared; in Case 9, several months before and in Case 10, five years before. Because involvement of the artery tends to be focal, vascular disease cannot be excluded by a negative biopsy, even one in which the tissue is sectioned serially. Yet despite this, only three of thirteen patients with neuritis (Cases 18 to 20) could not be shown on biopsy to have arteritis. Within this limitation of the biopsy method, therefore, one seems justified in concluding that in patients with rheumatoid arthritis peripheral neuritis is associated either with the sudden appearance de novo of an arteritis that is necrotizing or with

Table VIII
RELATIONSHIP OF PERIPHERAL NEURITIS TO ARTERITIS

Type of Arteritis	No. Patients with Neuritis	No. Patients Without Neuritis
Necrotizing	8	3
Non-necrotizing	2	4
Biopsy negative	3	11

the appearance of necrosis in a previously existing but non-destructive form of arteritis. (Table VIII.) Necrotizing arteritis may occur at sites other than the vessels to the peripheral nerve as was the case in three patients (Cases 11, 14 and 15) who did not have peripheral neuritis.

The clinical features of peripheral neuritis in these patients are outlined in Table IX. Neuritis was usually sudden in onset; patients often experienced their first symptoms after a period of sleep. In the majority of the group marked motor as well as sensory loss developed. In contrast to the patients of Irby, Adams and Toone [32], pain from neuritis was not striking except in two patients (Cases 3 and 4). Rather, anesthesia was noted in the skin segment supplied by the nerve. The neurologic defect was usually marked, involving distal segments of one or more extremities. Undoubted lesser degrees of involvement were not as readily detected. Occasionally, low grade fever, marked anemia and leukocytosis with a shift to the left accompanied the reaction. There was no evidence of a concomitant exacerbation of the patients' synovitis. Rather, the patient usually appeared to have suffered an isolated assault upon a peripheral nerve. The full development of the neuritis took place often within the day of onset. Symptoms of the neurologic deficit in most cases remained stationary for several weeks or months, followed by gradual return of function within the year. Such a period would be compatible with regrowth of a peripheral nerve. When corticosteroids were continued there was no apparent inhibition of the recovery process. This pattern of maximum damage at the outset followed by slower improvement correlated well with the histologic picture of arteritis. Biopsy specimens taken within the first month revealed acute arterial inflammation; those taken subsequently, even as early as a month later (Cases 1 and 2), already showed beginning healing.

While this description could be applied to

TABLE IX

NEUROLOGIC FEATURES IN SIXTEEN PATIENTS WITH RHEUMATOID

ARTHRITIS AND PERIPHERAL NEURITIS

Case No.	Arteritis	Duration of Arthritis Before Neuritis (yr.)	Steroid Therapy Before Neuritis (mo.)	Symptom of Neuritis	Steroid Therapy After Neuritis (mo.)	Outcome of Neuritis
1	Necrotizing	6	10	Quadriplegia	6	Residual paralysis
2	Necrotizing	11	74	Bilateral foot drop	1	Progressed to death
3	Necrotizing	26	20	Quadriplegia	4	Residual paralysis
4	Necrotizing	1	8	Bilateral foot drop	1	Improvement paralysi
5	Necrotizing	15	0	Bilateral foot drop	0	Recovery
6	Necrotizing	11/2	12	Left foot drop	16	Recovery
7	Necrotizing	7	40	Numbness hand, toe	8	Recovery
8	Necrotizing	8	24	Numbness fingers	24	Recovery
9	Non-necrotizing	2	0	Eyelid weakness	0	Recovery
10	Non-necrotizing	12	0	Numbness left ulnar area, arm	0	Recovery
18	Negative	7	44	Bilateral foot drop	10	Residual paralysis
19	Negative	15	0	Extensor communis paralysis	0	Recovery
20	Negative	28	26	Numbness fingers	41	Recovery
32	No biopsy per- formed	14	56	Left foot drop	3	Progressed to death
33	No biopsy per- formed	7	0	Left foot drop	0	Recovery
34	No biopsy per- formed	71/2	6	Long extensor thumb paralysis	4	Recovery

most of the patients, several pursued a more relentless course. Two of the sixteen patients with peripheral neuritis (Cases 2 and 32) probably died of disseminated arteritis. Both had enlarged spleens during life. Widespread visceral involvement was demonstrated in Case 2; autopsy was refused in Case 32 but death occurred four months after the onset of the neuritis during which time the patient, already severely crippled by her arthritis, rapidly deteriorated. She had progressive shortness of breath, fever and increasing anemia. Although other patients (Cases 1, 3 and 18) had severe neurologic disease and did not recover function of the involved part, it was postulated that the arteritis healed (as could be demonstrated at autopsy twenty months later in Case 1) but that the extent of nerve and possibly muscle damage was too great to permit return of function.

Serum Rheumatoid Factor Test. The titers of the serum rheumatoid factor were reviewed to determine if the patients with arteritis had more elevated values than those without arteritis. This relationship has been noted by others [17,21]. In the sheep cell agglutination test performed on

the serum euglobulin fraction, a test that causes agglutination in a titer of 1:14 or higher is considered positive [82]. It is unusual for a titer to exceed a value of 1:224 or 1:448. In both groups of patients the results of the test varied from barely positive to markedly elevated values. (Tables III and v.) The lone exception was the patient (Case 10) who had undergone a complete remission of her arthritis and who had a negative reaction to the test. Many patients in both groups, but especially those in the group with arteritis, tended to have higher titers. The highest value (1:896) was achieved repeatedly by a patient (Case 20) who had a negative biopsy and by one (Case 4) who had arteritis. Yet, while not true in every case, there seems to be a tendency in this series for patients with arteritis to have higher values.

Positive L.E. Cell Test with Necrotizing Arteritis. The reaction to the L.E. cell test was positive in four of ten patients with necrotizing arteritis. In none of three patients with non-necrotizing arteritis and in only one of thirteen patients (Case 27) with no evidence of vascular disease on biopsy was the result positive.

Table x

Chronologic relationship of pericarditis, episcleritis and positive l.e. factor

to peripheral neuritis and necrotizing arteritis

Case No.	Pericarditis	Episcleritis	L.E. Factor
1	0	9 to 12 months after A and N	0
2	9, 7, 6 years before A and N	2 years before A and N	0
3	3 years before A and N	0	0
5	0	6 to 9 months after A and N	0
6	0	10 months before A and N	4 months after A and N
7	0	0	4 to 6 months before A and N
8	0	0	3 years after A and N
9	2 years before N	0	0
11	Same time as A	3 years before A	Same time as A
23	0	4½ years before negative biopsy	0
27	0		11/4 to 21/4 years after negative biops

Note: A = necrotizing arteritis; N = peripheral neuritis; 0 = symptom absent or test negative.

The L.E. cell test was routinely performed in our clinic to determine the incidence of this abnormality in our rheumatoid population [18] and not because of unusual clinical features that the patient might have shown. An exception was a patient (Case 11) in whom features of disseminated disease developed for which an L.E. cell test was made and found positive. Under these conditions of almost random testing there was little temporal correlation in the same patient between a positive L.E. cell reaction and other findings suggestive of necrotizing arteritis as peripheral neuritis and episcleritis. (Table x.) Also biopsy was not performed at the time of either an L.E. cell test or development of episcleritis as was the case when peripheral neuritis occurred since we were not then aware of their possible significance. Data are not available, therefore, to show whether or not other episodes of necrotizing arteritis actually occurred at the time of each of these events. Such a possibility is suggested because of the association of a positive L.E. cell reaction or episcleritis almost exclusively in patients with necrotizing arteritis.

Comparison of Patients with Arteritis Collected from the Literature and from This Series. The available literature was searched for examples of arteritis in patients with rheumatoid arthritis. (Table XI.) The survey undoubtedly is incomplete. Only patients in whom arteritis was proved anatomically have been considered. Sources that did not give sufficient information to identify individual patients were not included [52,67,79]. Although there may be a relationship between vascular inflammation and the development of rheu-

matoid granulomas [70], patients who had only granulomas without definite arteritis were excluded. It was hoped thereby to be able to relate clinical findings to a specific proved pathologic diagnosis.

A total of eighty-one patients was found and pertinent features of the group analyzed. For purposes of tabulation, if the author made no mention of a clinical finding in a case history that otherwise was quite complete it was assumed that the particular finding probably was searched for but was absent. However, patients reported by Lewis [43], Graef [24], Levin [44], Radnai [55], Taubenhaus [75] and Stolzer [73] and their coworkers were excluded from many of the tabulations since they were too briefly described. Only laboratory tests for rheumatoid and L.E. factors, anemia and proteinuria that were actually recorded were tabulated.

Vasculitis is a relatively uncommon complication in rheumatoid arthritis. As is shown in Table xI, the majority of the patients have been described as case reports of but one or a few patients. Sometimes they have been recorded as a small part of a much larger series of patients with rheumatoid arthritis [35,44,71,73]. Careful studies reveal a much higher percentage of arterial lesions, many in a subclinical form [69].

Most patients with rheumatoid arthritis and arteritis have been reported only within the last decade, a period which also has seen the introduction and widespread use of corticosteroid drugs. For this reason it is not surprising to find that 55 per cent of the collected patients have had previous treatment with these drugs. This was

Table XI

PATIENTS COLLECTED FROM THE LITERATURE WITH RHEUMATOID ARTHRITIS AND ARTERITIS
PROVED ON BIOPSY

Author, Reference, Year of Publication, Case No.	No. of Patients	Male Patients	Mean Age at Onset of Arthritis (yr.)	Mean Duration of Arthritis Before Biopsy (yr.)	Steroid Therapy Before Biopsy	Necrotizing Arteritis	Subcutaneous Nodules	Eye Inflammation	Hypertension	Clinical Pericarditis	Peripheral Neuritis	Perforation of Gastrointestinal	Peripheral Gangrene	Rheumatoid Factor*	L.E. Factor*	Anemia (less than 12 gm.)*	Proteinuria*
Lewis [43] 1934, Case 19	. 1	0	2	?	0	?		1	1				1				1/1
Ellman [16] 1948, Case 1	. 1		45	3	0	1	1							1	1	1/1	1
Graef [24] 1949					0	2											
Edwards [15] 1950, Case 7			37	4	0	0				4.4.5							
Case records M. G. H. [10] 1951.		0	59	5	0	1			0		1				1/1		1/1
Haas [26] 1951		0	56	4	0	1	1	1	1							1/1	1/1
Pirani [54] 1951, Case 2		1	6	16	0	1										1/1	1/1
Sokoloff [77] 1951, Cases 1, 3		1	47	0.5	0	0	0			0				1/2		0/1	
Levin [44] 1953		5			3	3					1	2					1
Liversedge [45] 1953		0	45	13	0	1			1		1					1/1	1/1
Nystrom [57] 1953		0	33	13	0	3	3				2				1/1	1/3	100
Radnai [55] 1953, Cases 1, 2, 3	. 3	1	50	7	?	2	1										
Robinson [57] 1953		2	38	9	3	0	1	2	1	1	4					2/4	100
West [78] 1953		1	33	2	1	1			1	1		1			1		1
Ball [4] 1954, Cases 1, 2, 3, 4		3	55	5	1	4	3	1	2		2			3/3	0/1	3/3	0/4
Bevans [6] 1954, Case 1		0	41	10	1	1	1	1	0	1	1			1/1		1/1	1 11
Finck [19] 1955		1	39	5	1	1			1		1			1/1			1/1
Taubenhaus [75] 1955	1	1	46	15	1	1											***
C.P.C. Washington University [13]		0	45	2					0						0./4	4./4	0./0
1956	1	0	45	2	1	1		1	0		1				0/1	1/1	1/1
Sinclair [64] 1956, Cases 1, 3, 4, 6,	9	2	(0)	7	0	-										0.00	6 10
9, 10, 11, 12, 14	1	1	60	10	0	?	3	1	5	1						8/9	5/9
Skogrand [65] 1956, Case 1 Bywaters [9] 1957, Cases 1, 2, 5, 9	4	2	36	6	1	2	4	1	1 2	1	1			4/4	9/3	1/1	1/1
	1	1	42	14	0	1		-		1	1		4	4/4	1/3	1/4	2/4
Fisher [20] 1957	1	1	53	11	1	1	1		1		1			1/1		1/1	1/1
Kemper [35] 1957	4	2	43	12	4	4		1	1		3		1	1/1	0/1	1/4	4.2.4
Rotstein [61] 1957, Case 2	1	1	26	11	1	1	0		0		1				0/1	0/1	0/1
Sokoloff [69] 1957	10	5	39	8	7	7	10	1	4	2	3			6/7	0/7	3/10	
Stolzer [73] 1957	1	2		-	1	1	1				1	1					
Irby [32] 1958, Cases 1, 3, 4	3	3	35	17	3	2	3	1	0		3		2	2/2	0/3	1/3	14.7
Case records, M. G. H. [11] 1959	1	1	24	25	1	1			0	1	1			1/1	0/1	1/1	
Epstein [17] 1959, Cases 1, 2, 4, 5,														./.	0/1	./.	
7, 9	6	3	43	10	6	6	6				5			6/6	3/6		
Johnson [33] 1959, Cases 1, 2, 3	3	1	50	2	3	3	1		1		3		2		1/3		1/3
Parker [53] 1959	3	3	35	11	3	3	1					3	1		0/1	1/3	1/3
Sum of findings	81	28	43	8.5	43	57	40	11	22	8	36	5	10	26	7	30	18
No. of patients observed for finding	81	76	75	75	78	71	71†	71†	71†	71†	71†	71†	71†	28‡	31‡	54‡	42‡
Per cent of patients with finding	100	37			55	80	56	15	31	11	51	7	14	93	23	56	43
This series, Cases 1 to 17	17	7	46	9	11	11	14	5	6	5	10	0	1	15	4	11	4
Per cent of 17 patients with finding	100	41			65	65	82	29	35	29	59	0	6	94	31	65	24

*These data are listed as the number of times the test was abnormal over the total number of tests performed.

† Data from patients reported by Lewis, Graef, Levin, Radnai, Taubenhaus, and Stolzer not totalled for this observation due to incomplete case histories; in the other reports, the observation was considered to be absent even though not specifically mentioned since the case histories were otherwise fairly complete.

Data totalled only from case histories in which they are specifically recorded as either present or absent.

true in an even higher percentage of our patients. It is perhaps even more pertinent that almost half of the group (45 per cent) had never received this medication prior to the discovery of their arteritis. When one distinguishes between necrotizing and non-necrotizing arteritis, one notes a stronger coincidence of steroids with a necrotizing lesion. There were fifty-five patients whose arteritis was necrotizing about whom

information concerning previous steroid therapy was available. Forty-one had received these drugs, an incidence of 75 per cent. Our experience was similar in this regard. Yet necrotizing arteritis has occurred in the absence of these drugs. Fourteen of the fifty-five patients with necrotizing arteritis collected from the literature had never received these drugs and had equally extensive vascular disease.

In other respects also there was agreement between the observations made in our clinic and the tabulation of cases from the literature. There was the usual higher incidence in females that is found in rheumatoid arthritis. The mean age of onset was in the mid-forties, a figure not at variance with that expected in this disease [63]. Arteritis did not supervene until an average of almost nine years of joint disease had elapsed. By this time advanced joint changes had developed in most patients. Anemia was present in over half the group; tests for rheumatoid factor were positive in almost all the patients. About a third of the patients had hypertensive blood pressure readings but except in a few instances hypertension did not seem to contribute to the severity of the illness. Proteinuria was observed in a larger number (43 per cent) of patients from the literature than in our group (24 per cent). However, this figure may be falsely high since it is quite likely that such a routine test as urinalysis was carried out in some additional cases and not reported because it was normal.

It was of interest to see how patients compared in the incidence of symptoms related to the vascular component of their disease. Both patients from our series and to a lesser degree those from the literature had a higher percentage of subcutaneous nodules, eye inflammation, clinically diagnosed pericarditis and peripheral neuritis than one expects in rheumatoid arthritis [63]. Useful but less common signs that marked the appearance of vascular disease were areas of gangrene of the tips or even the whole of the digits and perforation of an intestinal viscus. Only one of our patients (Case 3) had ulcers of the leg possibly due to arteritis.

We had noted that only episcleritis and peripheral neuritis tended to occur more often with the necrotizing form of arteritis. In the literature pericarditis that was diagnosed clinically occurred in six patients with necrotizing arteritis and in two with non-necrotizing arteritis; eye inflammation (iritis, episcleritis and Sjögren's syndrome) in six and four; subcutaneous nodules in thirty and six; and peripheral neuritis in twenty-nine and seven, respectively. Since there were a total of seventy-one patients with arteritis, necrotizing in fifty-seven instances and non-necrotizing in fourteen instances, it is apparent that each of the symptoms mentioned is almost proportionally divided between the two forms of arteritis. Thus the literature did not suggest that, of itself, necrosis

of the arterial wall bears a relationship to these symptoms.

The reaction to the L.E. cell test was positive in 23 per cent of the cases recorded in the literature (seven of thirty-one patients); in all but one of these seven patients the arteritis was necrotizing. Thus in this regard, too, there is agreement with our series of patients, most of whom had necrotizing arteritis if they had positive reactions to L.E. cell tests.

COMMENTS

There is little doubt that the disease under consideration is rheumatoid arthritis, despite the arteritis. The characteristic subcutaneous nodules and the serum rheumatoid factor found in almost all the patients are incontrovertible evidence of this disease. In addition, the majority of patients had typical, advanced joint changes evident clinically and on roentgenograms. One therefore must explain the arteritis, both necrotizing and non-necrotizing, as a lesion that has occurred in a patient with undisputed rheumatoid arthritis. Either a secondary, perhaps related, complication not previously present in the patient has arisen or a pre-existing and essential lesion in the pathogenesis of rheumatoid arthritis has been activated into an overt form. Of course, variations of these hypotheses are possible but basically they narrow down to whether arteritis in sites other than joint tissues is part of the underlying mechanism of this disease or not.

Does analysis of the findings of these patients lend support to either of these possibilities? This question cannot be answered finally on the basis of the evidence at hand. To do so would require knowledge about factors that cause and perpetuate the rheumatoid process that are not known. Some inferences can be made, however, based on our observations and those in the literature. Two objections are present, we believe, against the view that arteritis observed in non-articular sites plays a fundamental role in the pathogenesis of rheumatoid arthritis. They are, (1) the late appearance in so few patients with the rheumatoid process of arteritis and symptoms that reflect arteritis, and (2) the failure of the synovial and articular disease to become clinically active when the arteritis becomes manifest.

A critical piece of information that is lacking which would contribute to this problem is the exact incidence and type of arteritis present in patients with rheumatoid arthritis. As was

noted earlier, vasculitis occurs in but a small fraction of the group [14,35,71]. Yet the true extent of vascular changes is probably greater than the amount of disease actually found. A negative biopsy does not rule out an arterial lesion [48,77]. The vascular lesion, even though disseminated throughout the body, is focal in nature; it can be missed even when serial sections are made of the tissue. We have observed changes in the vessel wall limited to less than 100μ of its length. Yet, despite these handicaps, one is impressed with the difficulty in detecting arteritis, if one assumes it is a fundamental lesion, except in the small segment of the rheumatoid population that is described in this report.

An attempt to delineate the natural history of arteritis in rheumatoid arthritis can be made, based upon the evidence obtained clinically and at biopsy. The patient in whom it occurs is an arthritic in whom marked changes in his joints have already developed. The onset of the arteritis is an abrupt event, often occurring within a matter of hours. Prodromal symptoms are not apparent. The lesions vary in extent from localized to widely disseminated areas, as shown at autopsy or by the magnitude of the clinical signs. But irrespective of their spread, they all tend to appear within a short time of several days or perhaps weeks. If the assault proves to be massive or involves a critical area, death or irreversible damage, especially to nerve trunks and possibly other tissues, result. Healing of the vascular inflammation begins within several weeks and possibly sooner. Even if the patient dies following overwhelming arteritis, the vessels on examination already show evidence of repair. It is quite likely that further episodes occur, as evidenced by the subsequent appearance of some of the symptoms that have been associated with arteritis. Again, these too subside. The conclusion that can be drawn from this summation is that arteritis is a new feature that has been added to the picture which in its recognizable form has not existed previously in the patient.

The preceding analysis is based upon the necrotizing form of arteritis. It has been difficult to form an opinion concerning the relationship of this type to non-necrotizing arteritis. In any one biopsy specimen we have usually observed one type of lesion even though several vessels were involved. However, in Case 1 of the present series the initial biopsy specimen showed necrotizing arteritis; subsequent biopsy speci-

mens showed some vessels manifesting healing necrotizing arteritis and others which were typical of non-necrotizing arteritis. The association of some clinical and serologic findings with necrotizing arteritis suggests a difference between the two types of arteritis. These were peripheral neuritis, episcleritis and positive reactions to L.E. cell tests. However, except for the last reaction no such association could be firmly established from a tabulation of cases recorded in the literature. Thus, while one can speak with more assurance regarding events produced by necrotizing arteritis, no firm statement can be made about non-necrotizing arteritis. It is of interest that two patients biopsied by Sokoloff, Wilens and Bunim ([71], Cases 9 and 10 this report) had non-necrotizing arteritis but did show signs of peripheral neuritis thereafter. Unfortunately, biopsy was not repeated at that time.

In addition to the appearance of new symptoms in the patient as evidence of a new reaction, one is impressed by the lack of exacerbation of the pre-existing joint disease. In none of the patients under our care was there a flare of synovial and periarticular tissues except as might be expected when steroids sometimes were reduced in amount. If the argument is accepted that a basic lesion of rheumatoid arthritis is activated, one might anticipate that increased inflammation of some or all of the involved joints would also be noted. Many of the patients had active joint disease, the degree of which it is often difficult to quantitate, but even so, no obvious changes took place. Indeed, in Case 1 observers were stuck by the diminution of warmth and swelling as well as pain in the joints of the limbs involved by peripheral neuritis.

Opposed to the view that arteritis in sites other than joint tissues is not intrinsically related to his rheumatoid disease is the concept that in every patient with rheumatoid arthritis alterations occur in the vascular system as part of the pathogenesis of the disease. This underlying, fundamental role played by the vascular system then is thought to become activated extraarticularly in some patients. Sokoloff et al. [70] have shown by careful examination of the early subcutaneous nodule that necrotizing arteritis can be found in many of these lesions. These authors suggest that the arterial lesion is a primary event and that further development of the rheumatoid granuloma may subsequently mask the initial arteritis. It should be possible, if this hypothesis is correct, to detect arteritis in

every lesion of the patient with rheumatoid arthritis if a sufficiently early and thorough examination is performed. Of eight patients with rheumatoid arthritis who came to autopsy, Sokoloff [69] reported arteritis in seven. This experience is not borne out by others [4,35,64], although such meticulous examination of autopsy tissues is not often carried out. Our data do not rule out this hypothesis although lack of association of the overt vascular disease with activation of existing articular disease and the absence of arteritis in many rheumatoid patients are points against its acceptance.

A completely satisfactory explanation for the occurrence of arteritis in rheumatoid arthritis has so far not been found. Most writers who have reported such cases are inclined to attribute its greater, recent incidence to the use of corticosteroid drugs. For reasons mentioned in the analysis of these drugs in our series and those from the literature it does not seem likely to us that this explanation will suffice for all patients. Still, the possibility cannot be entirely excluded since the occurrence of this complication has been noted more frequently after the introduction of the corticosteroid drugs. Precise data are not available, however, and it is conceivable that greater attention than before is now being paid to patients' complaints who have such a chronic illness because more effective drugs are at hand. Such a factor may account for some of the increased incidence. Kemper, Baggenstoss and Slocumb [35] found at autopsy widespread lesions similar to those of classic polyarteritis nodosa in four of fourteen rheumatoid patients who had received corticosteroids; none were found in thirty-eight patients who had not received these drugs. In the latter group, however, there were three patients with active panarteritis limited to one organ and in two cases to one vessel. Kulka, Ropes and Bauer [41] noted at autopsy that of twelve rheumatoid patients who had evidence of vasculitis, six had received these drugs and six had not. The lesions in the patients treated with hormones differed from those not so treated principally in a greater predilection for arteries and arterioles and a relative preponderance of neutrophils over mononuclear cells. These authors suggested that corticosteroids had intensified the vascular inflammation which they regarded as associated with the basic disease process of rheumatoid arthritis. The data in our report and from the literature do not negate and perhaps lend partial support for

this hypothesis but also suggest that it cannot be the sole explanation since widespread arteritis has also developed in patients who never had received these drugs.

One is tempted to speculate about the significance of the serologic reactions in these patients. Such features as the high incidence of subcutaneous nodules and juxta-articular bone erosions, commonly seen in our patients, were those that have been noted by Ziff [81] to be associated with higher titers of the serum rheumatoid factor. The titers of this abnormal globulin tended to be considerably elevated in many of our patients but slightly more so in the group with arteritis. In two instances of low and absent titers (Cases 9 and 10) the only test performed had been made several years after the biopsy and at a time when the patient's disease had become inactive. Other workers have stressed the relationship between vasculitis and unusually high titers of the rheumatoid serum agglutinating factor [17,21].

Although the number of positive reactors in our series was small, four of ten patients with necrotizing arteritis had positive reactions to L.E. cell tests. A similar relationship was found in the survey of the literature. Only one of thirteen patients without arteritis and none of three with non-necrotizing arteritis from our group had this reaction.

The meaning of this abnormality in these patients is unclear. Only one of our patients (Case 11) would have been considered to have acquired lupus erythematosus although some of the systemic symptoms found in some other patients have been described in that disease. Episcleritis was noted in two of 105 patients with disseminated lupus erythematosus at the Johns Hopkins Hospital and clinical pericarditis in a higher, although unstated, percentage [29]. Polyneuritis has not often been recorded as a specific neurologic abnormality [62] although findings of injury to the central nervous system are more frequent [29].

Positive L.E. cell tests have been found in various surveys to occur in a small percentage of patients with definite rheumatoid arthritis [18,23,37]. None of these patients were reported to have been biopsied so that the incidence of vasculitis was not evaluated. Other patients have been described with positive reactions to L.E. cell tests, rheumatoid arthritis and vasculitis. Ogryzlo [52] noted that four of eight patients with diffuse systemic rheumatoid disease had

positive test results. These patients were not identified as individual case reports so that one cannot correlate the tests with arteritis or the type of arteritis. In another report [1] necrotic ulcers developed on the lower part of the legs in six patients with rheumatoid arthritis and subcutaneous nodules. Biopsy of the ulcer margins disclosed what appeared to be a rheumatoid nodule that had broken down. No arteritis was mentioned but its presence cannot be excluded as a likely cause of the tissue ischemia. Four of these six patients had L.E. cells. Slocumb [66] has mentioned vasculitis and the presence of L.E. cells in the blood of patients with rheumatoid arthritis during the withdrawal of steroid treatment.

The L.E. cell is produced by an interaction of patient's abnormal serum gamma globulin and nuclear materials [31]. Similar serum abnormalities have been noted in Sjögren's disease [30]. It was therefore of interest that two rheumatoid patients with necrotizing arteritis described in the literature [26,65] and one of our patients (Case 10) with non-necrotizing arteritis had Sjögren's disease.

Damage to blood vessels, frequently small arteries, arterioles and capillaries, is characteristic of the pathology of disseminated lupus erythematosus as noted by Klemperer, Pollack and Baehr [39]. These vascular changes are marked by necrosis of the vessel wall similar to the arteritis seen in our patients. In an earlier and less extensive study by these same authors the same changes were thought to represent proliferating lesions in the lining endothelium with bland thrombi obstructing the lumen [2]. Lesions of this latter type were described by Bywaters [9] in patients with rheumatoid arthritis who had digital necrosis due to vascular inflammation.

It would seem that in some rheumatoid patients with arteritis there is an association between vascular inflammation and the presence of certain abnormal gamma globulins. This association was not present in every patient with arteritis but is almost absent in the group in whom vascular lesions could not be demonstrated; such an association obviously does not prove that a causal relationship exists. Lately, evidence has been brought forth that in patients with lupus erythematosus globulins exist with the characteristics of antibodies that are directed against components of cell nuclei [31]. The rheumatoid factor also is a gamma globulin of

larger molecular size but, while it may be an antibody, its role in this regard has not been adequately described. If the presence of these serum factors is indeed related to arteritis, then assuming that such factors function as antibodies it is conceivable that arteritis in patients with rheumatoid arthritis may represent an immunologic response. Such a theory would be compatible with the clinical picture that has been described in our patients; that is, the development at some point in the course of the rheumatoid patients' disease of an acute episode, often transient and self-limited. This episode, one might speculate, may be induced by an antigen-antibody interaction. This explanation does not account for the presence of rheumatoid factor in the large majority of patients with rheumatoid arthritis who do not have arteritis. The only difference between such patients and those with arteritis that has been noted is the possibly greater elevation of rheumatoid factor titer in the group with arteritis, a point not well substantiated by our data although recognized in other studies. As more information about the basic mechanism in diseases like rheumatoid arthritis is discovered, it should be possible to establish these clinical and pathologic data upon a firmer basis.

SUMMARY

The clinical and pathologic features of seventeen patients with rheumatoid arthritis and histologically proved arteritis were examined and compared with the findings in fourteen other patients with arthritis who had a negative biopsy. Of the seventeen patients with arteritis, eleven had a necrotizing lesion. The reports of an additional eighty-one patients with arteritis, described in the literature, were surveyed for comparison with those of the present study.

Several findings were more commonly associated with the patient with necrotizing arteritis. These included a higher incidence of episcleritis, peripheral neuritis and the serum L.E. factor. The presence of these findings is suggestive evidence of necrotizing arteritis. Subcutaneous nodules and clinically diagnosed pericarditis were noted equally in patients with either type of arteritis but infrequently in the patients with a negative biopsy.

No precipitating factors for arteritis were found. Evidence for the suggestion that the use of corticosteroids is related to this complication is not convincing, although more cases of

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necrotizing arteritis have been reported in the era after cortisone; the data lend some support to the suggestion that in some patients corticosteroid may promote transformation of nonnecrotizing to necrotizing arteritis.

The data do not finally answer the question whether arteritis, especially of the necrotizing type, is a fundamental event in the pathogenesis of arthritis or, alternatively, that arteritis and arthritis are diverse manifestations of rheumatoid disease.

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The Mild Hemophilias*

Occult Deficiencies of AHF, PTC and PTA Frequently Responsible for Unexpected Surgical Bleeding

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PATIENTS with congenital AHF, PTC or PTA† deficiencies but normal whole blood clotting times may be conveniently referred to as examples of mild hemophilia. These patients have a lesser degree of specific clotting factor deficiency than those with prolonged clotting times, and usually fewer symptoms, but occasionally they bleed severely, particularly following trauma. The name "occult hemophilia" perhaps would be more appropriate since the disease is not detectable by the traditional prolonged clotting time.

Graham, McLendon and Brinkhous [1] have suggested that patients with mild AHF deficiency have an allelomorphic form of hemophilia due to an allele hm distinct from h, which is responsible for severe hemophilia. The allele hm then permits production of AHF but not in amounts sufficient for effective hemostasis. They also suggested that the AHF level in both normal subjects and in patients with hemophilia is determined by a continuous series of isoalleles. This would account for the wide range of concentrations found in normal subjects as well as for different grades of severity of the disease. A similar explanation might be employed for the inheritance of variable degrees of PTC and PTA deficiency.

Although there were occasional reports in the not too recent literature of hemophiliac patients with normal clotting times, a marked

† AHF indicates antihemophilic factor, factor VIII, antihemophilic globulin (AHG), antihemophilic factor A (AHF—A), alpha prothromboplastin. PTC indicates plasma thromboplastin component, factor IX, antihemophilic factor B (AHF—B), beta prothromboplastin, Christmas factor. PTA indicates plasma thromboplastin antecedent, antihemophilic factor C (AHF—C).

prolongation was considered characteristic of the disease [2,3]. In 1947 Quick [4] devised the prothrombin consumption test and demonstrated that it was impaired in a subject with hemophilia. In a series of twenty-four patients [5] in whom diagnosis was based on family history or impaired prothrombin consumption he found seven with normal clotting times. In 1950 Merskey [6] found the clotting time normal in ten and slightly prolonged in 11 of 72 patients with hemophilia. The diagnosis in the mild cases was based on the failure of the patients' blood to correct fully the prolonged clotting time of blood from patients with severe hemophilia. He found prothrombin consumption impaired in 75 per cent and normal in 25 per cent of the mildly affected patients. In 1953 Graham et al. [1] investigated a family in which there was mild hemophilia; of seventy-nine living members (3 generations) fourteen males were affected. Their AHF levels, determined by a method based on the partial thromboplastin time, ranged from 9 per cent to 25 per cent of normal. In 1957 Pitney [7], in studying a group of sixty-five patients with AHF deficiency, correlated the symptomatology and laboratory findings in nineteen patients with normal clotting times. Their concentrations, determined by a thromboplastin generation method, ranged from 3 per cent to 38 per cent of normal.

In 1952 and 1953 hemophilia B (PTC deficiency) and hemophilia C (PTA deficiency) were distinguished from classic hemophilia (AHF deficiency) by Aggeler et al. [8], White, Aggeler and Glendening [9], Biggs et al. [10] and Rosenthal, Dreskin and Rosenthal [11]. Biggs and Macfarlane [12] in 1958 reported

^{*} From the Hematology Research Laboratory, Children's Hospital, San Francisco, California. This study was supported by U. S. Public Health Service Grant No. H-2754.

normal clotting times in fifty-one of 138 patients with hemophilia A and in thirteen of twenty patients with hemophilia B. In the former group the concentration of AHF ranged from zero to 49 per cent and in the latter the concentration of PTC was zero to 20 per cent. Bolton and Clarke [25] in 1959 found normal clotting times in eight of twelve patients with hemophilia B. The PTC concentrations ranged from 10 to 72 per cent. The specific factor assays by these authors were based on thromboplastin generation methods. Ikkala [13] in a survey of hemophilia in Finland published in 1960 classified his patients according to the degree of specific factor deticiency. Among a group of 109 patients he found the following: nine with mild (AHF over 10 per cent), eleven with moderate (AHF 5 to 10 per cent) and sixty-two with severe (AHF 0 to 5 per cent) hemophilia A, eighteen with mild (PTC over 8 per cent) and nine with severe (PTC under 3 per cent) hemophilia B. According to this classification the patients with normal clotting times included six with severe, seven with moderate and eight with mild hemophilia A and one with severe and fourteen with mild hemophilia B. The titrations of AHF were made by a thromboplastin generation method and the PTC assays were performed with a modification of the partial thromboplastin test. The occurrence of mild PTA deficiency has been noted by many observers including Biggs and Macfarlane [12] and Rosenthal et al. [14].

All previous investigators have noted the striking susceptibility to hemorrhage following surgical procedures in these patients and have remarked that spontaneous bleeding phenomena such as hemarthrosis and hematuria are rare. A similar degree of specific factor deficiency has been found among different affected members of the same family in all instances so far investigated.

The diagnosis of hemophilia A, B and C (AHF, PTC and PTA deficiency) is based primarily on the results of two laboratory procedures: the Quick prothrombin test and the thromboplastin generation test. A brief schematic outline of blood clotting is given in Figure 1. It is noted that tissue thromboplastin will substitute for AHF, PTC and PTA in all clotting reactions. The Quick prothrombin test, in which the clotting time of recalcified plasma containing an optimum quantity of tissue thromboplastin is determined, therefore remains normal when there is a deficiency of these

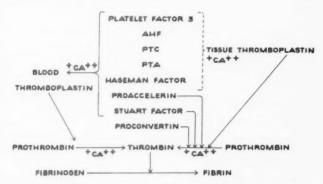


Fig. 1. Schematic representation of the blood coagulation mechanism.

factors. On the other hand, the thromboplastin generation test, which measures the production of blood thromboplastin, will be affected if the concentration of any one of them is reduced. Although other clotting factors affect the results of the test, its greatest usefulness is found in the differential diagnosis of AHF, PTC and PTA deficiencies. A reduced concentration of proaccelerin or Stuart-Prower factor can be eliminated from consideration if the Quick prothrombin time is normal, and by specific assays for these factors. Platelet factor 3 can be eliminated by the substitution of a cephalin suspension for platelets in the test. Hageman factor need not be considered since a deficiency of this factor does not cause hemorrhagic symptoms. Vascular hemophilia usually can be eliminated if the patient has a normal bleeding time. The thromboplastin generation test allows for the differentiation between as well as the detection of relatively small deficiencies of AHF, PTC and PTA. Suspected deficiency of AHF or PTC can be confirmed by further assay procedures. There is as yet no accurate method for assaying PTA.

In the present investigation a detailed clinical and laboratory study was made of forty-six patients with mild hemophilia observed in the Hematology Research Laboratory of the San Francisco Children's Hospital.

MATERIALS AND METHODS

Selection of Cases. Since 1952 the hematology laboratories of the San Francisco Children's Hospital and of the Stanford Medical School have cooperated in the investigation of patients with blood coagulation disorders. Most of the definitively diagnosed cases in Northern California have been investigated in one of these laboratories. The combined statistics are shown in Table 1.* Of the total of 149 patients with

* We are indebted to Dr. Theodore Spaet and Dr. Judith Pool for permission to use the data from the Stanford Medical School coagulation laboratory.

Table 1
COMBINED YEARLY STATISTICS FOR THE DIAGNOSIS
OF HEMOPHILIA (AHF, PTC AND PTA DEFICIENCY)

Normal Prolonged Clotting Clotting Time Time Total No. Year of Cases No. % No. % 1952 0 100 1953 7 14 6 86 1 1954 21 5 24 16 76 42 1955 26 11 15 58 1956 13 23 10 77 3 1957 19 59 41 32 13 1958 22 11 50 50 11 1959 22 17 77 23 5 149 67 45 82 Total 55

Note: The patients reported on in Tables 1 and 11 were diagnosed at the Children's Hospital and Stanford Medical School Coagulation Laboratories, San Francisco, California.

AHF, PTC or PTA deficiency approximately half have been of the mild variety. The proportion of patients with a mild form of this disease has steadily increased; the total number of new patients seen per year has been relatively constant. As previously noted by others [12,13] the majority of patients with hemophilia A have severe deficiencies, in contrast to hemophilia B where most of the cases are mild. (Table II.)

Only those patients seen in the Hematology Research Laboratory of Children's Hospital were included in this series. Among 336 patients referred to the laboratory seventy-six were found to have hemophilia. Of the thirty who had prolonged clotting times twenty-six were AHF deficient and four PTC deficient. Of the forty-six who had normal clotting times twenty-four were AHF deficient, fifteen PTC deficient, and seven were thought to be PTA deficient. At the time of examination all patients were ambulatory, not bleeding, and had not recently been transfused.

Technical Methods. Collection of blood specimens: All blood was drawn by clean venipuncture using the two syringe technic. The blood in the first (uncoated) syringe was used for various plasma determinations, for serum in the thromboplastin generation test and for blood counts. The blood in the second (silicone coated) syringe was used for the clotting time, prothrombin consumption test and PTC assay. One milliliter of blood was also drawn into a third syringe containing platelet diluting fluid (0.2 ml. of 40 per cent formalin in 100 ml. of 3.8 per cent sodium citrate). Five milliliters of blood for fibrinogen deter-

Table II FREQUENCY OF VARIOUS TYPES OF HEMOPHILIA

Type of Hemophilia		Clotting me	Prolonged Clotting Time		
тепорина	No.	%	No.	%	
A	37	35	68	65	
В	20	59	14	41	
C	10	100	0	0	

mination was mixed with 0.1 cc. of 33 per cent potassium oxalate. All other blood to be used for plasma determination was mixed with 3.2 per cent sodium citrate in 0.7 per cent sodium chloride in a proportion 9:1. The plasma was usually stored for several days at minus 20°c.

Coagulation Time. As modified from Pohle and Taylor [15], 1 ml. of blood was placed in each of five glass tubes of 13 by 100 mm. in diameter in a waterbath at 37°c. Starting at three minutes all tubes were tipped at one minute intervals. The clotting time of each tube was recorded from the completion of venipuncture until the tube could be inverted after tapping lightly in the horizontal position against the waterbath. The times obtained with each of the five tubes were averaged. The normal range in this laboratory for the method is 5 to 12.5 minutes.

Prothrombin Consumption. Two milliliters of blood was placed in each of three glass tubes of 13 by 100 mm. in diameter. The tubes were capped with Parafilm and inverted once in such a manner that the blood was exposed to the entire internal surface of the tube. After one hour at 37°c., 0.2 ml. of 3.2 per cent sodium citrate in 0.7 per cent sodium chloride was added to each tube. The clots were rimmed, the tubes centrifuged and the serum pooled and incubated for 30 minutes at 37°c. The prothrombin concentration of the serum was determined and was expressed as a percentage of the patient's plasma prothrombin. Plasma and serum prothrombin concentrations were determined by the method of Hjort, Rappaport and Owren [16]. This test may also be influenced by a deficiency of Stuart-Prower factor but since the concentration of the latter was normal in the plasma of all patients included in this group and since its concentration remains unaltered in the serum the test, as used in these investigations, can be considered as specifically measuring prothrombin. The normal range in this laboratory for the residual serum prothrombin is 10 per cent to 25 per cent of the patient's plasma prothrombin value.

Plasma "prothrombin" time (prothrombin complex activity). This was determined by the method of Quick [17].

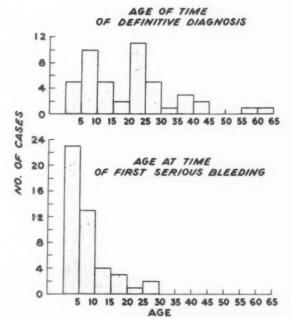


Fig. 2. Age distribution at the time of first serious bleeding and at the time of definitive diagnosis in forty-six patients with mild hemophilia.

The Thromboplastin Generation Test. This was performed by the method of Biggs and Douglas [18] with the following modifications: the serum was incubated for 18 to 24 hours at 37°c. as recommended by Bergsagel [19]. A dilute cephalin suspension prepared by the method of Bell and Alton [20] was used in place of platelets in all tests. In all cases the serum and plasma were stored for several days at minus 20°c. before the tests were performed. The diluted serum was kept in an ice bath for 30 minutes before performing the tests.

PTC Assay. This was performed by the method of Stapp [21]. The test must be performed with meticulous attention to all details given in the original publication. It is particularly important to use a cephalin suspension of high potency prepared according to the method of Milstone [22]. We have found that both normal and test specimens can be stored at minus 20°c. for several months without loss of potency. In this test PTC deficient plasma, cephalin and adsorbed beef plasma are used as substrate. We found this method to give highly reproducible results. The normal range in our laboratory is 70 to 130 per cent.

AHF Assay. This was performed by the method of Pool and Robinson [23]. This method which gives highly reproducible results is an adaptation of the thromboplastin generation test. The normal range in our laboratory is 50 to 140 per cent.

RESULTS

Age. The age distribution at the time of definitive diagnosis and at the time of the first serious bleeding episode is shown in Figure 2.

TABLE III
SEX INCIDENCE IN FORTY-SIX PATIENTS WITH MILD
HEMOPHILIA

Data	AHF	PTC	PTA
Male	24	15	5
Female	0	0	2
Total	24	15	7

A significant number of patients with the mild form of the disease had their first bleeding episode in adolescence or adult life. This later onset of symptoms usually occurred in patients who had not had severe trauma or surgical procedures in their earlier years. Although in many instances the first bleeding episode occurred in early childhood, its significance was not fully appreciated and the possibility of an underlying hemorrhagic disease was not entertained until subsequent bleeding tendencies appeared years later.

Sex and Heredity. The sex incidence is shown in Table III. As was to be expected, there were no females in the group of patients suffering from AHF or PTC deficiency. Both males and females were represented in the group of PTA deficient patients. The data regarding the family history is shown in Table IV. In twenty-one of thirty-nine patients with AHF or PTC deficiency the family history was consistent with the expected sex-linked recessive hereditary transmission. Three additional patients with AHF deficiency and two with PTC deficiency gave a history of a bleeding tendency in one brother but in no other member of the family. In eleven patients with AHF or PTC deficiency a family history of bleeding disorder could not be elicited, and in two patients no family history was available. Three of the patients with PTA deficiency

Table IV
Family History in patients from forty-one
Families with mild hemophilia

Data	AHF	PTC	PTA
Sex-linked recessive	11	7	0
Male sibling only	2	1	0
Dominant	0	0	3
No family history	7	4	3
History unavailable	1	1	1
Total	21	13	7

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FAMILY HISTORY OF BLEEDING TENDENCY 63

PERSONAL HISTORY: SURGICAL BLEEDING 100

EASY BRUISING AND HEMATOMATA 63

PROLONGED BLEEDING 55

HEMARTHROSIS 41

EPISTAXIS (SEVERE) 33

GASTRO-INTESTINAL 25

GENITO-URINARY 7

* In thirty-six of forty-six patients, or 78 per cent of total, surgery was performed.

Fig. 3. Symptoms in forty-six patients with mild hemophilia.

had family histories consistent with a dominant transmission of the trait, three had no family history of bleeding, and in one adopted child a family history was not available. Among the group of forty-six patients there were forty-one families represented, since two pairs of brothers with PTC deficiency and two pairs of brothers and one grandfather and grandson with AHF deficiency were investigated.

The relatives of patients with mild hemophilia gave histories compatible with the mild form of the disease. In no instance did the family history suggest severe hemophilia. However, at least ten deaths from intracranial, pulmonary and gastrointestinal hemorrhage and bleeding following tooth extraction, tonsillectomy and prostatectomy occurred in affected members of the families.

Symptoms. The frequency of various symptoms in this group of patients is shown in Figure 3. The patients bruised easily and in some cases the formation of large subcutaneous or intramuscular hematomas after trauma occurred in 63 per cent of cases. However, the tendency to bruise easily was not severe and hematomas usually occurred only after reasonably severe trauma. Usually only one or two episodes were recorded in any patient's history. Prolonged bleeding from lacerations, which occurred in 55 per cent of cases, was likewise not a very troublesome complaint.

Only 41 per cent of the patients had ever had a hemarthrosis. Of these a few had one or two attacks. The majority had three to ten and one patient approximately twenty attacks. It did not occur spontaneously in early childhood, as in severe hemophilia, but in later life, usually as the result of distinct trauma. It seldom involved

TABLE V
THE INCIDENCE OF SURGICAL BLEEDING IN FORTY-SIX
PATIENTS WITH MILD HEMOPHILIA

Type of Surgery	No. of Opera- tions	No. with Bleed- ing	No. without Bleed- ing
Oral:			
Tooth extractions	26	25	1
Ear, nose and throat:			
Tonsillectomy and adenoidectomy	18	16	2
Abdominal:			
Gastrectomy	3	3	0
Appendectomy	4	1	3
Herniorrhaphy	3	3	0
Other:			
Orchidectomy	1	1	0
Vasotomy	1	1	0
Circumcision (as adults)	2	2	0
Neurolysis with transplant	1	1	0
Total	59	53	6

more than one or two joints and rarely resulted in permanent joint damage.

Gastrointestinal bleeding occurred in twelve members of this series. Nine had responded to medical management. Most had required blood transfusion at one time or another. In the three patients who were operated upon the bleeding was severe and intractable.

One third of the patients gave a history of repeated attacks of epistaxis, usually in child-hood but sometimes persisting into adult life. Only three patients had experienced gross hematuria. One had had three bouts and the other two only a single episode each. In all instances the bleeding was of less than two weeks' duration.

The hemorrhagic symptoms were sufficient to mark some of these patients as unmistakable "bleeders." Even so, their histories did not suggest either the degree or frequency of bleeding commonly found in severe hemophilia. A significant number of patients had never bled spontaneously. All patients, however, had bled when subjected to surgery.

The types of operations performed are shown in Table v. Hemorrhagic complications occurred in fifty-three of fifty-nine procedures. Twenty-five of twenty-six patients bled after tooth extraction and sixteen of eighteen after tonsillectomy and adenoidectomy. All patients who had undergone both procedures had bled from at least one. The number of operations for tooth extraction in the individual patient varied from one to four. Bleeding following these operations was usually of the slow persistent type lasting from one to four weeks. The

onset of bleeding was sometimes delayed for several days after the operation. In a number of cases it was severe enough to require transfusion. Acute hemorrhage during or several hours after operation occurred in only a few cases.

Three patients with AHF deficiency had partial gastrectomies for persistent severe bleeding from sources in the upper gastrointestinal tract which were never clearly identified. Two of these had previously been investigated in our laboratory and were found to have levels of 18 and 35 per cent, respectively. Both had gastrointestinal and intraperitoneal bleeding post-operatively, received massive treatment with whole blood and plasma and died from complications associated with the bleeding. The third patient, whose AHF level was 25 per cent, gave a history of having bled severely following a partial gastrectomy many years previously but has not bled since.*

Hemorrhage from the wound and into adjacent tissues following herniorrhaphy occurred in three patients. Curiously, no abnormal bleeding occurred in three of four patients who had appendectomies. Of the three who did not bleed one had 29 per cent AHF, one 37 per cent PTC, and one had PTA deficiency. All had shown other evidences of a moderate bleeding tendency and two had positive family histories. The relative infrequency of bleeding following this operation has been noted by other observers [7,12].

There was insufficient information to determine the incidence of bleeding from circumcision in the neonatal period. When a history of hemorrhage from circumcision in infancy was obtained, and in the two patients who had this operation in adult life, bleeding was neither severe nor unduly prolonged.

We have supervised management of bleeding following eight of the fifty-nine operations performed on these patients. These included four tooth extractions, two gastrectomies, one tonsillectomy and adenoidectomy, and one hernior-rhaphy. In all AHF deficient patients fresh frozen plasma stored not longer than two weeks or fresh whole blood was administered. In the PTC deficient patients ordinary blood bank blood and plasma were used. It has been stated that little bleeding should occur if the specific factor can be kept at a level of 30 per cent or

PROTHROMBIN
CONSUMPTION
(RESIDUAL SERUM
PROTHROMBIN IN %
OF PT'S PLASMA)

45

80

70

26

45

80

70

18

40

MEAN
NORMAL

Fig. 4. Clotting time and prothrombin consumption in forty-six patients with mild hemophilia. ● = mild AHF, ▲ = mild PTC, ■ = mild PTA, ○ = severe AHF, △ = severe PTC. Shaded area represents normal range.

more [12]. In our experience in the treatment of surgical bleeding in hemophilia a great deal more depends upon the skill of the surgeon and the type of operation than upon the level of the specific factor maintained in the blood of the patient. Hemorrhage after the removal of impacted or infected teeth or from suture lines in the gastrointestinal tract may prove far more difficult to control than bleeding from a very large abdominal wound. For example, some of our patients with specific factor levels above 30 per cent bled profusely despite supplemental preand postoperative plasma transfusions. Others, with lower levels, who were not treated preoperatively had less bleeding which either subsided spontaneously or after relatively small amounts of plasma.

Laboratory Findings. By definition the bleeding, clotting and Quick prothrombin times were normal and the thromboplastin generation test was impaired in every member of this group. In addition the results of the capillary fragility test, platelet count and fibrinogen concentration were normal in all cases. The plasma prothrombin, proaccelerin and Stuart-Prower factor concentrations were determined in most patients and found to be normal. The range of clotting times and serum prothrombin concentrations is shown in Figure 4. The residual serum

^{*}We have recently observed another patient with a slightly prolonged clotting time and AHF level of 6 per cent who has survived this operation after a very stormy postoperative course.

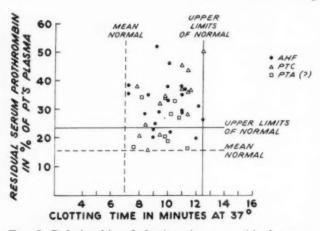


Fig. 5. Relationship of clotting time to residual serum prothrombin in forty-six patients with mild hemophilia.

prothrombin was normal in 25 per cent of the patients and slightly to moderately increased in the remainder. In no instance was it markedly increased to the degree commonly found in severe hemophilia. In Figure 5 it is seen that there is no significant correlation between the clotting time and the residual serum prothrombin concentration in the mildly deficient patients.

The results of the thromboplastin generation test in mild AHF deficiency are shown in Figure 6A. In most patients the degree of abnormality, particularly after six minutes' incubation, is not as great as commonly found in severe AHF deficiency. The most nearly normal time (10.3 seconds) was found in one patient (V. T.) in whom the AHF concentration was 29 per cent and who had had ample evidence of a bleeding tendency. In all patients in this group the substitution of normal serum for the patient's serum in the generating mixture failed to affect the results of the test while the substitution of normal plasma resulted in a normal value after six minutes' incubation.

The results of the thromboplastin generation test in patients with mild PTC deficiency are shown in Figure 6B. The results are similar to those found in mild AHF deficiency except that the substitution of normal plasma in the generating mixture was without affect while the substitution of normal serum resulted in normal values.

The specific assay values for AHF and PTC are shown in Figure 7. They range from 8 to 37 per cent in AHF deficiency and 9 to 58 per cent in PTC deficiency. Within this range we found no significant correlation between the degree of abnormality in the thromboplastin generation test and the specific factor assay

value. There was only a poor correlation between the severity of symptoms and the degree of specific factor deficiency. Using the same assay methods, we have found less than 5 per cent of the clotting factors in all patients with markedly prolonged clotting times and 3 to 15 per cent in patients with slightly prolonged clotting times.

The results of the thromboplastin generation test in the seven patients thought to have PTA deficiency are shown in Figure 8. In all instances the substitution of normal serum for the patient's serum resulted in normal values. The substitution of normal plasma for the patient's plasma improved thromboplastin generation in each instance but did not result in normal values in three of the seven cases. These results are consistent with a diagnosis of PTA deficiency. However, since there is not a good method for assaying PTA in mild cases the diagnosis cannot be entirely certain. The assay values for AHF and PTC in this group of patients (Table vi) suggest that a deficiency of one or both of these factors may have affected the results of the thromboplastin generation test in some instances.

COMMENTS

In most hemophiliac patients with prolonged clotting times hemorrhagic symptoms begin in early childhood. There are frequent spontaneous hemarthroses, often leading to permanent damage to the joint, repeated attacks of hematuria, and numerous episodes of internal and external bleeding following slight trauma. Hematemesis and melena, intra-abdominal and retroperitoneal hemorrhage and retropharyngeal and laryngeal hemorrhage are not uncommon. Few patients with overt hemophilia are subjected to surgery except for tooth extraction and then only in the most urgent situations, and with full knowledge of the hazards involved. Surgical morbidity and mortality is high. The limitations imposed by the disease often result in many economic and social problems.

By contrast, the onset of symptoms in a significant number of patients with occult hemophilia is delayed until late childhood or adult life; the symptoms are milder and less frequent. Few of these patients consider themselves to be "bleeders." The financial burden of their illness is negligible and they suffer no social or economic discrimination because of it. An amazing number of them have been subjected to surgical

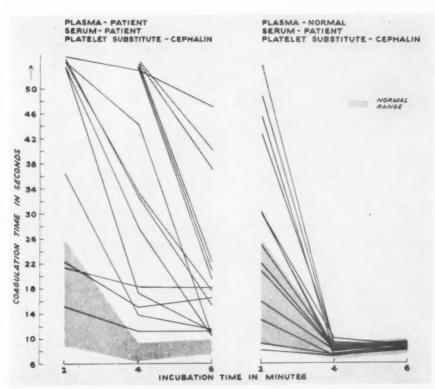


Fig. 6A. Thromboplastin generation tests in patients with mild AHF deficiency.

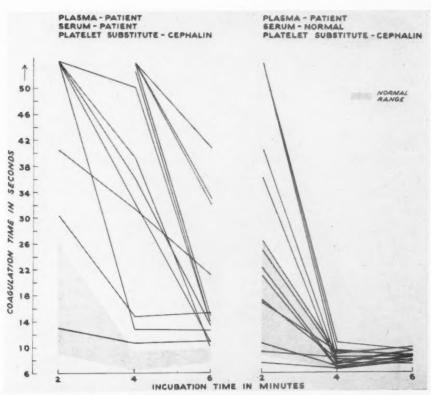


Fig. 6B. Thromboplastin generation tests in patients with mild PTC deficiency.

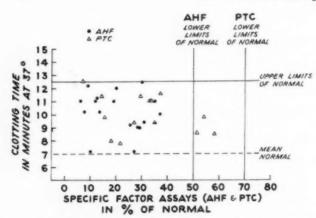


Fig. 7. Specific assay values in mild AHF and PTC deficiencies.

operations from which almost all have bled. The amount of bleeding has varied but in a significant number it has been quite severe and in a few has led to death.

If the surgeon is forewarned the hazards of operation can be lessened by meticulous attention to hemostasis at the time of surgery and the

TABLE VI
AHF AND PTC CONCENTRATIONS IN PATIENTS
THOUGHT TO HAVE PTA DEFICIENCY

Case	PTC	AHF
1, E. J.	76	25
2, G. C.	83	52
3, D. A.	63	31
4, W. R.	54	43
5, I. McC.	50	107
6, K. N.	68	61

liberal use of plasma and whole blood. However, in our opinion there is a risk of postoperative bleeding in any hemophiliac patient, mild or severe, even when large amounts of plasma are used. Surgery in all hemophiliacs can not be performed with safety until concentrated extracts of the necessary clotting factors are available.

One of the most serious surgical problems

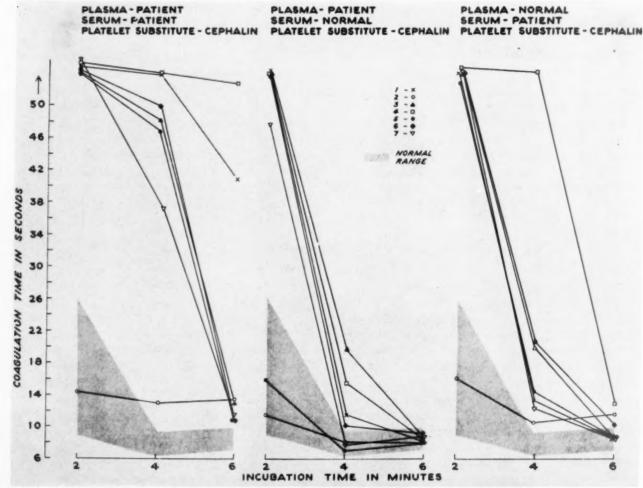


Fig. 8. Thromboplastin generation tests in patients with suspected PTA deficiency.

presented by these patients is persistent massive hemorrhage from the upper gastrointestinal tract. When this becomes life endangering, surgical exploration and partial gastric resection might be carried out with the hope of removing the source of the bleeding, reducing the erosive action of gastric acid, and partially devascularizing the gastric remnant. Even if gastrectomy is performed the patient may continue to bleed. When this occurs it is difficult to determine whether the hemorrhage originates from a lesion missed at the original operation, from the suture lines, or from an entirely new site. There is also the danger of postoperative intraperitoneal hemorrhage due to a bleeding vessel unnoticed at the time of operation or due to a loosened ligature. In view of the many difficulties involved we would advise extreme conservatism in the management of upper gastrointestinal bleeding in hemophilia.

The performance of so many operations in this group of patients implies the general mildness of their hemorrhagic symptoms. On the other hand, preoperative investigation and interrogation frequently must have been inadequate. In some instances the patients were quite aware of hemorrhagic symptoms either in themselves or in their families but the surgeon was unaware of it or ignored it because the "routine" clotting time was normal. The frequency of surgical bleeding in this series casts considerable doubt on the value of "routine" preoperative clotting time. We agree with Diamond and Porter [24] that it is more likely to provide a false sense of security than to detect potential occult bleeders.

In general, the severity of symptoms in the relatives of patients with mild hemophilia is of the same order as that observed in the patients themselves. When one considers that these symptoms were often not spectacular or disabling, it seems probable that some of the patients may have been unaware of similar symptoms in their relatives. The high percentage of patients in this series giving positive family histories is therefore quite remarkable. This appears to indicate that by careful questioning it is possible to uncover a family history of bleeding as frequently in the mild as in the severe cases.

In recent years the number of patients found in our laboratory to have severe hemophilia has decreased while the number with the mild forms of these diseases has increased. It is our impression that a large proportion of the patients with more severe symptoms residing in this area have been included in our survey but that there is still a large group of patients with the mild form of the disease not diagnosed in the community. The data suggest that mild cases may be more prevalent than severe ones.

In the diagnosis of mild hemophilia the greatest reliance must be placed on a careful history and physical examination. In any suspected case complete coagulation studies should be performed. The finding of impaired prothrombin consumption is of some value but the abnormality shown by this test may be relatively small and in approximately 25 per cent of cases the results are normal. Under these circumstances attempts to establish a definite diagnosis by observing the effect on prothrombin consumption of the addition of serum, adsorbed plasma or the plasma of patients with severe deficiencies of AHF, PTC or PTA are usually unsuccessful. Partial thromboplastin and thromboplastin generation screening tests were performed in only a few of the patients in this series. However, we found several subjects with normal values by these methods who had definite abnormalities in the thromboplastin generation and specific assay tests. It is our impression that a meticulously performed thromboplastin generation test is superior to all other methods in the diagnosis of mild hemophilia and that, as performed in our laboratory, it is capable of detecting all patients who have a significant reduction in the specific factor

Specific assays for AHF and PTC are useful in confirming abnormalities observed in the thromboplastin generation test. Until an accurate assay method for PTA is available some doubt must be entertained as to the validity of the diagnosis of PTA deficiency when it is based solely on the results of the thromboplastin generation test.

SUMMARY

A detailed clinical and laboratory study was made of forty-six patients with hemophilia A, B or C (AHF, PTC or PTA deficiency) in whom the venous whole blood clotting time was normal.

In all patients thromboplastin generation was impaired.

The incidence of positive family histories was as great as is usually found in the severe forms of the diseases. The first episode of severe bleeding was often delayed or ignored until adolescence or adult life.

Surgical bleeding, particularly after tonsillectomy or tooth extraction, was the most frequent symptom. Episodes of spontaneous bleeding such as hemarthrosis and hematuria were far less frequent than in the severe cases.

The concentration of AHF in mild hemophilia A ranged from 8 to 37 per cent, and of PTC in hemophilia B from 9 to 58 per cent. There was only a rough correlation between the specific factor assay values and the severity of symptoms in this group of patients.

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Studies on the Relationship of Temperature to Sickle Cell Anemia*

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THE high viscosity of sickle cell blood of low oxygen saturation has been demonstrated to be an important factor in the production of the thromboses which are responsible for many of the lesions associated with the disease [1,2]. The recent finding that there is low temperature, about 30°c, with consequent high viscosity, in the superficial venous blood of the lower leg [3,4] prompted the present study, which was undertaken to determine the viscosity of sickle cell blood at the cool condition of the lower extremity. It seemed likely that the concurrence of the two factors of sickling and low temperature would cause excessively high viscosity, and therefore might help to explain the severity of the thrombotic processes in the lower leg which result in chronic skin ulcers, and which may be important in the pathogenesis of the pulmonary infarctions commonly seen in sickle cell disease [5,6].

METHODS

The subjects consisted of five patients with clinical evidence of sickle cell anemia, all of whom were homozygous for S hemoglobin on electrophoresis. The controls were an equal number of apparently healthy adults.

Blood viscosity was measured by a modification of the method of Ham and Castle [1,2]. Blood specimens were obtained in dry glass syringes from an antecubital vein and anticoagulated with "balanced" ammonium and potassium oxalate, which does not affect blood viscosity [7]. Six milliliter aliquots were placed in tonometers and equilibrated for thirty minutes with a gas mixture of 85 per cent nitrogen, 5 per cent oxygen, and 10 per cent carbon dioxide, after the technic of Lange, Minnich and Moore [8]. The blood was then transferred, under seal, to an Ostwald viscosimeter which had been flushed with the gas mixture. Both arms of the viscosimeter were connected through a Y-tube to a reservoir balloon which

contained approximately 30 L. of the gas. Viscosity was then determined at 37°c. and 30°c. by adjusting the temperature of a water bath in which the viscosimeter was immersed. The viscosity of each sickle cell specimen was tested at the same packed cell volume at which it was drawn, hereinafter referred to as the "in vivo hematocrit," and also at an hematocrit of 40 per cent, which was produced by plasma removal.

RESULTS

The findings, summarized in Table I, reveal that with a temperature drop from 37°C to 30°C there is a significant increase in the viscosity of normal blood, sickle cell blood at the *in vivo* hematocrit, and sickle cell blood at an adjusted hematocrit of 40 per cent. For each of these groups the observed increase in viscosity at the lower temperature is significant at the level of 6.25 per cent.

The data also show that the viscosity of the sickle cell blood at a hematocrit of 40 per cent is significantly higher (P < 0.01) than that of normal blood at both 37°c and 30°c. It is interesting to note that there is no significant difference between the viscosity of normal blood and that of sickle cell blood at the *in vivo* hematocrit (Fig. 1); this is true at both temperatures.

COMMENTS

Although the mean age of the control subjects was greater than that of the patients, this factor is not considered important since age, per se, does not influence blood viscosity [3]. The lower in vivo hematocrits and the higher blood viscosities at the adjusted packed cell volume of the children suggests that there may have been significant hematologic differences between the children and the adult patients. However, whatever these differences were, they did not affect

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Table I

THE EFFECT OF TEMPERATURE ON THE VISCOSITY (IN CENTIPOISES) OF NORMAL AND SICKLE CELL BLOOD

Case No.	Age (yr.) and		Viscosity of Normal Blood		Viscosity of Sickle Cell Blood "in Vivo Hematocrit"		Viscosity of Sickle Cell Blood Hematocrit at 40 Per cent	
	Sex		37°c.	30°c.	37°c.	30°c.	37°c.	30°c
				Norma	l Blood			1
IIIIIIV V	38,M 24,F 24,F 48,F 60,F	40 41 40 40 41	3.9 4.2 3.7 3.4 3.9	4.8 5.4 4.7 3.9 4.7				
				Sickle Ce	ell Blood			
I II III IV V	24,M 8,F 36,F 5,F 3,M	30 20 24 22 22			4.3 3.1 3.8 3.4 2.7	5.3 3.7 4.9 3.8 3.4	5.4 7.1 7.1 6.2 5.5	6.7 8.2 8.3 8.4 6.9
Iean tandar devia			3.8 ±0.30	4.7 ±0.53	3.5 ±0.62	4.2 ±0.86	6.3 ±0.83	7.7 ±0.86

the relationship between temperature and viscosity.

The demonstration of increased viscosity of sickle cell blood at low temperature takes on importance because of the previously mentioned finding of superficial venous blood temperature of about 30°c in the lower leg [3]. It would have been desirable to have measured the temperature in the greater saphenous vein of the subjects in the present study; but in each of the adults the veins had been thrombosed, and in the children they were too small to permit puncture. It seems reasonable to assume that the findings of the earlier study on superficial vein temperature would be applicable to these patients.

Because cooling shifts the oxygen dissociation curve of hemoglobin to the left, resulting in a higher degree of saturation at a given oxygen tension [9], one effect of low temperature is to reduce the percentage of sickle forms [10], and therefore to lower the viscosity of the blood. The studies reported herein, however, indicate that the direct effect of low temperature on raising the

viscosity of the fluid system offsets the effect on the oxygen dissociation curve, resulting in a marked net increase in the viscosity of the blood. Such a finding strongly indicates that in the lower extremity, in addition to the factor of stasis, which has been shown to cause lowered pO₂ and pH and increased sickling [11], the low temperature of the venous blood plays an important role in the local vicious cycle of erythrostasis.

Except for one subject (Case v), who was too young to give a reliable account, it is interesting that each patient stated that he experienced unpleasant symptoms within a few minutes of exposure to cold, such as going outdoors on a wintery day. The sensations described were those of aching in the extremities and malaise. In this connection it is pertinent to consider the fact that exposure to cold results in cooling of the superficial venous blood draining the skin and extremities [12], and therefore in locally increased blood viscosity. Such a relationship between environment, superficial venous blood

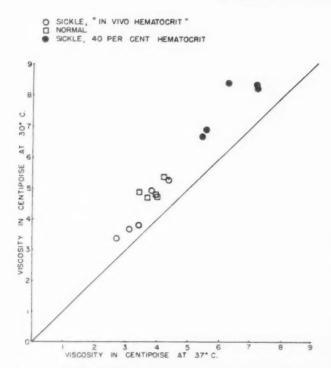


Fig. 1. The effect of temperature on the viscosity of normal blood and sickle cell blood at the hematocrit of the patient and at an adjusted hematocrit of 40 per cent (see text).

viscosity, and sickling, suggests that a cold microclimate might have an adverse effect on the condition of sickle cell blood in peripheral or superficial tissues. Conversely, a perennially hot climate would tend to allow superficial and peripheral blood to remain at or near core body temperature and viscosity levels. It is appropriate to point out that, with few exceptions [13], the world distribution of the sickle cell gene is equatorial (Fig. 2), the highest incidence being among tribes in central Africa and among the Veddoids of southern Arabia and southern India [14,15]. Indeed, the belt of highest incidence of sickle cell trait appears to correspond remarkably with the zone of highest sustained temperature throughout the year in inhabited Africa [14,16]. In addition to those anthropologic [14], sociologic [14] and epidemiologic [17,18,19] factors which may have allowed the deleterious gene to endure and which may be responsible for its limited geographic spread, tropical temperature may be a distinct advantage to the prolonged survival of the patient with the disease. The vicious cycle, commencing in the lower extremities, of erythrostasis, thrombosis, pulmonary infarction and eventual reduction in pulmonary diffusing capacity with decreased arterial pO₂ [20,21], should be less severe in

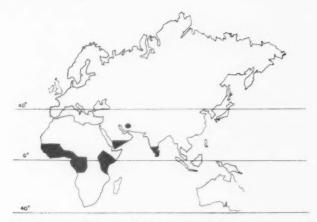


Fig. 2. The solid areas indicate the highest incidences of the sickling trait, after Lehmann [14]. Note the equatorial distribution in Africa and among the Veddoids in southern India and Arabia.

persons living in hot climates than in persons living in temperate or cold zones. The observations that the sickle cell trait is approximately three times as prevalent among African Negroes as it is among American Negroes [22], and that the survival rate to adulthood among the homozygotes is from 15 to 35 per cent [23] are consistent with the hypothesis that climate may play a role in the expression of the genetic disorder. It is furthermore suggested that any factor which lowers blood viscosity, such as other anemia or hypoproteinemia, should lessen the severity of those pathologic processes which are due to the high viscosity of sickle cell blood. Such disorders as nutritional deficiency and parasitism therefore, may operate to the advantage of the sickle cell patient.

Greenberg, Kass, and Castle [24] found in one patient that the viscosity of completely deoxygenated sickle cell blood at a hematocrit of 25 per cent, which they regarded as a typical level for the disease, was the same as for the blood fully oxygenated at a hematocrit of 50 per cent. In the experiments reported herein, the similarity between the viscosity of the oxygen unsaturated sickle cell blood at the actual hematocrit of the patients and the viscosity of equally unsaturated normal blood indicates that at the usual level of anemia sickle cell blood is no more viscous than normal blood. It would appear that the rate of erythrocyte destruction may be in part related to blood viscosity and that the rate of hemolysis proceeds to that degree of anemia which reduces the viscosity to levels near or below normal, at which point the rate of red cell destruction is, in turn, reduced.

JANUARY 1961

SUMMARY

1. The high viscosity of sickle cell blood, relative to normal blood at the same hematocrit, is further increased at cool temperature. Thus, in addition to the factors of pO₂, pCO₂, and pH, the thermal condition of a tissue, such as the cool superficial structures of the lower leg, is important in the localization of sickle cell disease lesions.

2. It is suggested that environmental temperature may play a role in the expressivity of the underlying genetic disease, and that climatic factors therefore may influence the world distribution of the trait.

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Jaundice in Hodgkin's Disease*

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Establishment of the cause of jaundice in the patient suffering from Hodgkin's disease often is difficult. This study was undertaken in the hope that analysis of a large series of jaundiced patients with Hodgkin's disease, seen at the Memorial Center during the period 1947–1957, might help clarify this problem.

REVIEW OF THE LITERATURE

The incidence of jaundice in patients with Hodgkin's disease as reported in the literature varies in most series from 3 to 8 per cent. (Table I.) (Beatty [34] reported an incidence of 57.5 per cent, Kilburn [57] 68 per cent in an autopsy series; Jackson and Parker [31] found an incidence of jaundice of 10 per cent in patients with hepatomegaly.) Beatty [34] found a male predominance of 4.3:1 in jaundiced patients suffering from Hodgkin's disease as compared to a ratio of 1.9:1 in the whole group of patients with Hodgkin's disease.

The older literature expressed the opinion, usually based on individual case reports, that jaundice in Hodgkin's disease is usually a result of common duct obstruction caused by involved lymph nodes [1-5,9,16-22,24]. Other possible mechanisms of jaundice in Hodgkin's disease were mentioned in 1920 [7]. Barron [8] in 1927 was the first to state that intrahepatic peribiliary infiltration produces jaundice more frequently than does pressure of enlarged nodes or tumor masses against the bile ducts. Muller and Boles [10] in 1927 pointed out that a dual mechanism may be at work in the production of jaundice in Hodgkin's disease, namely, intrahepatic involvement with disease and extrahepatic biliary obstruction. Caronini [11] in 1928 discussed the question of jaundice in Hodgkin's disease from a pathologic point of view. Her own

experience was based on six patients. Three of these had common duct obstruction or infiltration, two had liver involvement and pressure on the common duct, and one had liver involvement with Hodgkin's disease alone. She mentions nine references to cases in which the jaundice was attributed to pressure on the common duct only [1,4,16-22], four references to cases in which the jaundice was caused by common duct obstruction and intrahepatic involvement [12-15], and only one reference to a case in which the jaundice was attributed to intrahepatic lesions alone [23]. Beatty [34], in his series of twenty-three jaundiced patients with Hodgkin's disease who came to autopsy, found only two patients in whom extrahepatic biliary duct obstruction was the cause of jaundice. In the patients in whom the cause of jaundice was considered to be intrahepatic

Table I
Incidence of Jaundice in Hodgkin's disease as
REPORTED IN THE LITERATURE

Author	Total No. of Patients Studied	Per cent Incidence of Jaundiced Patients
Uddstromer [26]	548	8.0
Baker, Mann [27]	65	3.0
Goldman [28]	212	4.2
Goldman, Victor [29]	319	4.0
Jackson, Parker [30]	62	4.6
Hoster, Dratman, Craver,		
Rolnick [32]*		3.0 to 8.0
Beatty [34] †	40	57.5
Kilburn [57]†	22	68.0

* A review article.

† This series deals with deceased patients only.

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liver involvement, the lesions were fibrotic and

mainly in the portal trinities.

Jaundice in Hodgkin's disease may not be directly related to tumor masses. The occurrence of acquired hemolytic anemia in Hodgkin's disease is well documented [24,35,51-55]. In one series [54] of 104 cases, this syndrome was present in eight. However, jaundice caused by this mechanism alone is usually mild. Amyloid of the liver, secondary to Hodgkin's disease, has been described [34,58,59]. However, jaundice in amyloid of the liver is rare. Beatty [34] had one such case in his series, and Kilburn [57] published a report of a similar case. In the latter, however, there also was "rare periportal foci of Hodgkin's disease in the liver," and a "secondary hemolytic anemia may have been present." The occurrence of viral hepatitis in patients suffering from Hodgkin's disease has been mentioned [45,46]. Some observers have claimed that this infection has caused temporary remission of the disease [46]. Beatty [34] had one case which he classified as toxic hepatitis. Diamond [60] also mentioned the possibility of chlorpromazine and methyltestosterone hepatitis. Cirrhosis in jaundiced patients suffering from Hodgkin's disease has been mentioned by several investigators [3,34,56]. In one of Beatty's cases [34], posthepatitic cirrhosis was the only explanation for the jaundice. Anemia, pyrexia and toxemia have also been listed as contributing to the development of jaundice in Hodgkin's disease.

Laboratory Tests in the Differential Diagnosis of Jaundice in Hodgkin's Disease. The results of the ordinary liver function tests in this setting may be equivocal and confusing [36]. Sherlock [35] states that routine liver function tests are not usually sensitive enough to reflect changes resulting from cellular infiltration, but results of the bromsulfalein test may be abnormal in such patients as well as in patients with extrahepatic bile duct obstruction. Evaluation of the serum alkaline phosphatase is difficult in the presence of bone involvement. Electrophoretic analysis of the proteins shows that the alpha components are mainly involved, but this is common in other conditions with a rapid turnover [35].

The determination of serum glutamic oxaloacetic (SGO-T) and serum pyruvic transaminase (SGP-T) may help to establish the diagnosis of hepatitis and the presence of extrahepatic biliary obstruction [37,66]. Diffuse liver involvement with lymphomas does not usually cause a marked elevation of the serum SG-T; it is apt to be only slight, much lower than that observed in hepatitis [38]. In contrast to the lymphomas, carcinomas involving the liver cause an elevation in the SGO-T levels [38]. Serum lactic dehydrogenase (SLD) activity is elevated in infectious hepatitis in the early stages of the disease [70,71]. In comparison to the serum transaminase, SLD returns to normal more quickly in hepatitis and therefore its usefulness is limited to the first days of jaundice.

It cannot be overemphasized that the elevation of lactic dehydrogenase and transaminase in the serum is a non-specific phenomenon occurring in a variety of pathologic conditions other than liver disease. Therefore these changes can be evaluated only in conjunction with

other clinical and laboratory findings.

The preliminary data on leucine aminopeptidase (LAP) indicate that determination of this enzyme may be helpful in the differential diagnosis of jaundice, being increased in the serum of most patients with obstructive jaundice [72]. An increase in the serum and urinary activity of LAP has been found in patients with cancer of the pancreas [73]. In patients with malignant lymphomas (a series of eleven cases) an increased urinary activity was found; the serum activity in these patients was normal or only slightly elevated in ten. In one patient with malignant lymphoma invading the pancreas the serum LAP was markedly elevated [73]. Patients with infectious or toxic hepatitis, cirrhosis and hepatoma usually showed serum elevations that were generally of lesser degree than those in patients with cancer of the head of the pancreas.

Preliminary studies suggest that the determination of serum isocitric dehydrogenase (ICD) activity may be of value in differentiating between hepatocellular and extrahepatic obstructive jaundice, as well as in the detection of viral hepatitis and liver metastases [74]. In the early stages of viral hepatitis the increase of serum ICD activity was found to be from four to thirty times normal [74]. In cancers involving the liver the elevation was less marked and did not occur in all cases [74]. Elevations of serum ICD activity were found in Hodgkin's disease; lymphosarcoma; leukemias; carcinomas of the prostate, breast, lung, stomach, pancreas, colon and rectum; melanomas and osteogenic sarcomas involving the liver [74]. The serum ICD

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TABLE II
CLINICAL DIAGNOSES IN 101 JAUNDICED PATIENTS WITH
HODGKIN'S DISEASE

Diagnosis		Per cent*
Liver involvement with Hodgkin's		
disease	19	16.3
Homologous serum jaundice	12	10.3
Toxic hepatitis	4	3.4
Cholelithiasis	3	2.5
Passive congestion	2	1.7
Viral hepatitis	1	0.9
Choledocholithiasis	1	0.9
Amebic hepatitis	1	0.9
Metastatic liver carcinoma	1	0.9
No definitive clinical diagnosis of the		
type of liver disease made	57	49.0
	101	86.8

^{*} Of the whole series of 116 patients.

activity was found to be well within the normal range in patients with extrahepatic obstructive jaundice (six cases), cirrhosis (nineteen cases), and also in patients with a wide variety of conditions including myocardial infarction [74]. An increase in serum enzymes has also been reported in liver diseases; for example, marked elevations in malic dehydrogenase, phosphohexoisomerase [75], aldolase [76,77] have been observed in acute viral hepatitis.

Serum vitamin B_{12} levels have been found to be elevated in infectious and toxic hepatitis, and also in cases of liver carcinomatosis [40–43], with normal or only slightly elevated values in obstructive jaundice. In a small series of eleven patients with Hodgkin's disease normal levels of serum vitamin B_{12} were found [39]. The patients studied did not have known liver involvement due to Hodgkin's disease [44].

Liver biopsy was found to be helpful in establishing the cause of jaundice in patients with Hodgkin's disease even when all other diagnostic methods failed. However, a negative liver biopsy by no means excludes the presence of Hodgkin's disease of the liver [35,50-57].

PRESENT STUDY

The charts of 875 patients with Hodgkin's disease, all confirmed by biopsy, were reviewed. The cases were divided into two main groups: those in which the patients were alive at the time of the study (346 in number) and those in which the patients were dead at the time of the

Table III
SERUM BILIRUBIN DETERMINATIONS IN 103 JAUNDICED
PATIENTS WITH HODGKIN'S DISEASE

Serum Bilirubin (mg. %)	No.	Per cent*
1.5- 2.9	37	36.0
3.0- 5.9	21	20.4
6.0-9.9	12	11.6
10.0-19.9	20	19.4
20.0-29.9	6	5.8
30.0-39.9	7	6.8

^{*} Of the 103 patients examined.

study (529 in number). Of these 875 patients, 116 (13.3 per cent) had jaundice while followed up at the Memorial Center. In thirteen (11.2 per cent) the jaundice was clinically overt; in the remainder, the serum total bilirubin was 1.5 mg. per cent or higher. Of the 346 living patients, thirteen (3.8 per cent) were jaundiced; of the 529 dead patients, 103 (19.5 per cent) were jaundiced.

The causes of jaundice as determined during life fell into four categories: intra- or extrahepatic Hodgkin's disease, ninety-nine cases (85.4 per cent); hemolytic jaundice, eight cases (6.9 per cent); hemolytic jaundice and liver disease, two cases (1.7 per cent); cause unclear, seven cases (6 per cent).

Clinically, liver and/or biliary disease was the cause of jaundice in 101 (86.8 per cent) of the 116 jaundiced patients with Hodgkin's disease who were studied (116 = 100 per cent). The clinical diagnoses entertained in these 101 cases appear in Table II.

Serum bilirubin determinations were carried out in 103 patients (88.8 per cent); however, in not all of them was it performed during the period of maximum jaundice. The results are given in Table III.

The duration of jaundice varied from a few days to fifty-one weeks in the seventy-nine cases (68 per cent) in which reliable information was available. The median duration was two weeks. In 104 cases (89.7 per cent) jaundice was a preterminal event, in only twelve cases (10.3 per cent) did it occur at an earlier stage of the disease. In ninety-four cases (81 per cent) different modalities of therapy were given for Hodgkin's disease prior to the onset of jaundice.

Thirteen (11.2 per cent) of the 116 patients with jaundice were alive at the time of the study.

TABLE IV
AGE DISTRIBUTION IN 115 PATIENTS*

Age (yr.)	No.	Per cent
10-19	12	10.5
20-29	26	22.6
30-39	30	26.1
40-49	23	20.0
50-59	18	15.7
60-69	5	4.4
70-79	1	0.9

^{*} Age unstated for one patient.

In the remaining 103 patients survival from the first clinical symptoms that led to diagnosis to death ranged from four months to 381 months, with a median survival of thirty-five months. There was no difference in survival between males (seventy-two patients, 62 per cent) and females (forty-four patients, 38 per cent).

With the exception of one Negro all the patients were Caucasian. The youngest patient was fourteen years old when first seen at the Memorial Center, the oldest was seventy-two years old. In one case, the age was unstated. The age distribution is shown in Table IV.

Hodgkin's granuloma was diagnosed (biopsy) in 107 cases (92.2 per cent), Hodgkin's paragranuloma in six cases (5.2 per cent) and Hodgkin's sarcoma in three cases (2.6 per cent).

Many patients had multiple clinical abnormalities. The clinical abnormalities possibly

TABLE VI SIZE OF LIVER AND SPLEEN AS ESTIMATED DURING LIFE IN JAUNDICED PATIENTS WITH HODGKIN'S DISEASE

Size* (cm.)	1	Liver	ver Spleen	
Size (cm.)	No.	Per cent	No.	Per cent
No enlargement	16	13.8	44	38.0
Unknown	3	2.6		
Tip palpable only			9	7.8
1.0-1.9	13	11.2	8	6.9
2.0-2.9	14	12.0	6	5.2
3.0-3.9	19	16.4	12	10.6
4.0-4.9	15	12.9	10	8.6
5.0-5.9	3	2.6	7	6.1
6.0-6.9	10	8.6	7	6.1
7.0-7.9	9	7.8	5	4.3
8.0 or more	8	6.9	5	4.3
Below pelvic rim	6	5.2	3	2.6

^{*} Below the costal margin in the mid-clavicular line.

Table v
CLINICAL ABNORMALITIES RELATED TO JAUNDICE

Abnormality	No.	Per cent	
Fever	98	84.5	
Anemia	81	69.7	
Pruritus	48	41.4	
Ascites	35	30.1	
Dark urine	34	29.3	
Bleeding manifestations in the skin or			
mucous membranes	32	27.6	
Peripheral edema	31	26.7	
Light stools	26	22.4	
Abdominal pain or discomfort	21	18.1	
Indigestion	14	12.1	
Melena	9	7.7	
Abnormal sugar tolerance	9	7.7	
Pressure in right upper quadrant	7	6.0	
Hematemesis	6	5.1	
Fetor hepaticus	4	3.5	

related to the jaundice are listed in Table v in order of frequency.

Thirteen patients (11.3 per cent) did not have either a palpable liver or a palpable spleen during life. Sixteen patients (13.8 per cent) did not have a palpable liver and forty-four (37.9 per cent) did not have a palpable spleen. The size of the liver and spleen as estimated during life is given in Table vt.

Anemia (less than 11 gm. per cent of hemoglobin) was present in sixty-five cases (56 per cent). During the course of the disease anemia developed in sixteen additional cases (28.1 per cent). Leukocytosis (over 11,000 white blood cells per cu. mm.) was noted in twenty-nine cases (25 per cent) and leukopenia (less than 4,000 white blood cells per cu. mm.) in thirtyfour cases (29.3 per cent). In the rest of the cases, the white blood count remained within normal limits. A low platelet count (below 100,000 per cu. mm.) was found in thirty-two cases (27.6 per cent) and a high platelet count (over 350,000 per cu. mm.) was noted in nine cases (7.8 per cent). In the other cases, the platelet count was within normal limits. Macrocytes were seen in one case (0.86 per cent), target cells in one case (0.86 per cent) and normoblasts in one case (0.86 per cent).

A bromsulfalein test was performed in twentythree cases (19.8 per cent) and was abnormal in all of the patients tested. A serum alkaline phosphatase determination was made in ninetytwo cases (79.2 per cent of the series). The

following values were found: 1 to 3.9 Bodansky units, eighteen cases (19.6 per cent); 4 to 9.9 Bodansky units, twenty-one cases (22.8 per cent); 10 or more Bodansky units, fifty-three cases (57.6 per cent). A cephalin flocculation test was performed in ninety-nine cases (85.2 per cent of the series). The findings were as follows: normal, twenty-eight cases (28.2 per cent); 1 plus, eight cases (8.1 per cent); 2 plus, eleven cases (11.1 per cent); 3 plus, twenty-seven cases (27.3 per cent); 4 plus, twenty-five cases (25.3 per cent). The serum total cholesterol was determined in forty-nine cases (42.2 per cent of total series). The results were less than 100 mg. per cent in eleven cases (22.5 per cent of the forty-nine cases), 100 to 149 mg. per cent in twenty-two cases (44.9 per cent), 150 to 199 mg. per cent in eight cases (16.4 per cent), 200 to 299 mg. per cent in five cases (10 per cent) and more than 300 mg. per cent in three cases (6.2 per cent). Thymol turbidity was determined in eighty-four patients (72.5 per cent of the whole series). Normal values were found in fifty-eight cases (69 per cent) and abnormal values in twenty-six cases (31 per cent). The serum total protein was determined in ninety-nine cases (85.5 per cent of the total series). (The normal range in our laboratory is 6.5 to 7.9 gm. per 100 ml.) The values were 4 to 4.9 gm. per cent in eighteen cases (18.2 per cent), 5 to 5.9 gm. per cent in forty-one cases (41.4 per cent), 6 to 6.9 gm. per cent in twenty-two cases (22.2 per cent), 7 to 7.9 gm. per cent in fourteen cases (14.2 per cent) and 8 to 8.9 gm. per cent in four cases (4 per cent). Serum albumin determinations were obtained in seventy-five cases (64.5 per cent of the series). (Normal values in our laboratory are between 4.7 and 5.7 gm. per cent.) The results were 1.1 to 2 gm. per cent in one case (1.3 per cent), 2.1 to 3 gm. per cent in twenty-six cases (34.7 per cent), 3.1 to 4 gm. per cent in thirty-five cases (46.7 per cent), and 4.1 to 5 gm. per cent in thirteen cases (17.3 per cent). Serum globulin determinations were obtained in seventy-five cases (64.5 per cent of the series). (Normal values in our laboratory are between 1.5 and 2.5 gm. per cent.) The results were 1 gm. per cent or below in six cases (8 per cent), 1.1 to 2.2 gm. per cent in thirtythree cases (44 per cent), 2.1 to 3 gm. per cent in thirty cases (40 per cent) and 3.1 to 4 gm. per cent in six cases (8 per cent). SGO-T levels were determined in twenty-four cases (20.7 per cent of the series). Normal values were found in

TABLE VII
TYPE OF THERAPY IN NINE PATIENTS WHO RESPONDED
WELL TO THERAPY

Therapy	No. of Patients
Supportive treatment only	6*
TEM (triethylene melamine)	1
Radiotherapy and adrenocorticosteroids Radiotherapy, alkylating agents (nitrogen	. 1
mustard) and adrenocorticosteroids	1

^{*} In all these patients, the clinical diagnosis of hepatitis was made.

twelve cases (50 per cent), a slight elevation in nine cases (37.5 per cent) and a marked elevation in three cases (12.5 per cent).

Liver biopsy specimens were obtained in six cases (5.16 per cent of the total series) and in all instances demonstrated abnormalities. The findings, in general, correlated with the findings at autopsy when performed.

Therapy of Jaundice. The main types of therapy used were radiation to the liver and liver portal area, chemotherapy (mainly alkylating agents), adrenocortical steroids, general supportive measures and combinations of these. An evaluation of response to therapy of jaundice could be made in seventy-five cases (64.5 per cent of the total series). In nine (12 per cent) a definite regression of jaundice was observed following therapy. The type of therapy given in these cases is listed in Table vII. In three cases (4 per cent) the jaundice decreased markedly but did not disappear; and in the other sixtythree cases (84 per cent), no change in the intensity of the jaundice was noted following therapy.

Of the nine patients who responded well to therapy two were alive at the time of this study. Two of the seven deceased patients came to autopsy. The cause of jaundice in these two was hepatitis in one and obstruction of the common duct by adjacent lymph nodes, diffuse Hodgkin's disease and portal fibrosis in the other; the latter patient had been treated with nitrogen mustard and radiotherapy directed to the porta hepatis region.

The three patients who had a decrease but not complete disappearance of jaundice following therapy were all dead at the time of this study, and all came to necropsy. The pathologic findings in the liver were right hepatic and com-

TABLE VIII
TYPE OF THERAPY IN FOUR JAUNDICED PATIENTS WITH
HODGKIN'S DISEASE IN WHOM THERAPY POSSIBLY
HAD UNFAVORABLE EFFECTS

Therapy	Postmortem Diagnosis	Duration of Jaundice (wk.)
Radiotherapy, TEM, adreno- corticosteroids	Homologous serum	8
Radiotherapy, TEM and HN ₂ , adrenocorticosteroids	Periportal fibrosis and hemosiderosis	28
Radiotherapy, TEM	Choledocholithiasis, lymphangiomas and fatty metamorphosis	1
HN ₂ , adrenocorticosteroids	Marked fatty liver	2

mon duct obstruction by adjacent nodes invaded by Hodgkin's tissue, hepatic abscess, cholangitis, diffuse Hodgkin's sarcoma foci, and hemosiderosis in one case; healing viral hepatitis in the second case; and diffuse and nodular infiltration with Hodgkin's disease in the liver, fatty metamorphosis, invasion of the portal vein by tumor and partial obstruction of the hepatic vein in the third case. The first patient had been treated with surgery (choledochojejunostomy), chemotherapy (nitrogen mustard and TEM) and radiotherapy to the porta hepatis and hepatic region; the second was treated with cortisone; and the third was treated with radiotherapy directed to the region of the liver. Therapy, perhaps, had some unfavorable effects, as indicated in Table viii.

AUTOPSY SERIES

Of the 116 patients studied, fifty-seven (49.1 per cent) came to autopsy; forty (70.1 per cent) were males and seventeen (29.9 per cent) females. The youngest patient in the autopsy series was sixteen years old, the oldest was seventy-two years old. The age and sex distribution is given in Table IX.

The pathologic diagnoses in this group of patients, as made by biopsy during life, were Hodgkin's granuloma in fifty-four cases (94.7 per cent), Hodgkin's paragranuloma in two cases (3.51 per cent) and Hodgkin's sarcoma in one case (1.75 per cent). The final diagnoses at necropsy were Hodgkin's granuloma in forty-seven cases (82.5 per cent) and Hodgkin's sarcoma in ten cases (17.5 per cent).

During life a diagnosis relating to the nature of the liver involvement was made in seventeen cases (29.8 per cent of the autopsy series). The diagnoses were Hodgkin's disease involve-

TABLE IX

AGE AND SEX DISTRIBUTION OF FIFTY-SEVEN PATIENTS

WITH JAUNDICE AND HODGKIN'S DISEASE WHO

GAME TO AUTOPSY

Age (yr.)	Males	Females	Total		
Age (yr.)	Maics	remales	No.	Per cent	
10-19	5	1	6	10.5	
20-29	7	3	10	17.5	
30-39	10	3	13	22.8	
40-49	6	3	9	15.8	
50-59	9	5	14	24.5	
60-69	2	2	4	7.1	
70-79	1		1	1.8	
Total	40 (70.1%)	17 (29.9%)	57	100.0	

ment of the liver in ten cases (17.5 per cent of the autopsy series), viral hepatitis in six cases (10.5 per cent) and passive congestion in one case (1.8 per cent).

The pathologic findings at necropsy can be divided into four main groups: (1) extrahepatic bile duct obstruction as the sole cause of jaundice (two cases, 3.5 per cent); (2) extrahepatic bile duct obstruction and liver involvement with Hodgkin's disease (fourteen cases, 24.6 per cent), in these cases the extrahepatic obstruction was only partial and the bile ducts were not dilated above the lesion; (3) liver involvement with Hodgkin's disease without extrahepatic bile duct obstruction (twenty-six cases, 45.6 per cent); (4) causes other than due to tumor directly (fifteen cases, 26.3 per cent). (Table x.)

In the two patients with extrahepatic bile duct obstruction as the cause of jaundice the bile ducts were dilated above the obstruction; and the obstruction was caused by extrinsic pressure of involved nodes on the common duct. One of these patients did not have any pathologic changes in the liver; the other patient also had portal cirrhosis and passive congestion. In none of the patients with both extrahepatic bile duct obstruction and intrahepatic Hodgkin's disease (Table x1) were the bile ducts dilated above the lesion. In addition, a variety of incidental abnormalities were present in the liver. Forty patients in all (70.2 per cent) had intrahepatic Hodgkin's disease; however, in only twenty-six (45.6 per cent) was this the sole postulated cause of jaundice. Of the forty

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TABLE X

PATHOLOGIC FINDINGS IN THE LIVER OF FIFTEEN JAUNDICED
PATIENTS WITH HODGKIN'S DISEASE WHO DID NOT HAVE
TUMOR INVOLVEMENT IN THE LIVER OR EXTRAHEPATIC
BILE DUCTS*

Pathologic Findings	No. of Patients	Per cent of Total
Passive congestion	9	60.0
Fatty metamorphosis	5	33.2
Hemosiderosis	3	26.1
Atrophy of liver cells	3	26.1
Viral hepatitis	1	6.8
Toxic hepatitis	1	6.8
Portal hepatitis	1	6.8
Choledocholithiasis	1	6.8
Chronic cholangitis	1	6.8
Focal fibrosis	1	6.8
Lymphangiomas	1	6.8
Extramedullary hematopoiesis	1	6.8
Cloudy swelling	1	6.8
Central necrosis of liver cells	1	6.8
Hepatic cell edema	1	6.8
Bile stasis	1	6.8

^{*} Many patients had more than one abnormality hence the total exceeds 15 and 100 per cent.

patients, thirty-six had diffuse Hodgkin's disease in the liver, three had nodular metastases only, and one had diffuse and nodular lesions. The location of the lesions followed no consistent pattern; however, a greater number were found in the portal triads than anywhere else. All the patients with intrahepatic Hodgkin's disease also had a variety of other pathologic changes in the liver. Table XII lists miscellaneous abnormalities in the liver not directly related to tumor.

At necropsy, the liver weight varied from 900 to 4,500 gm., with a median weight of 2,500 gm. Six patients had a liver weighing less than 1,500 gm. (10.5 per cent of the series), nine over 3,000 gm. (15.8 per cent of the series). Of the fifty-seven patients autopsied, thirty-nine (68.4 per cent) had normal gallbladders at necropsy. In five, (8.8 per cent) Hodgkin's disease was found in the wall of the gallbladder. Hodgkin's disease, cholecystitis and cholelithiasis were found in one patient (1.8 per cent); chronic cholecystitis in three (5.3 per cent); choledocholithiasis in one (1.8 per cent); and distention of the gallbladder in one (1.8 per cent).

The spleen of all patients autopsied showed some pathologic changes. In forty-four cases JANUARY 1961

TABLE XI

TYPE OF EXTRAHEPATIC BILE DUCT INVOLVEMENT*

IN FOURTEEN JAUNDICED PATIENTS WITH

HODGKIN'S DISEASE

Туре	No. of Patients	Per cent of Total
Infiltration of common duct by Hodgkin's disease	2	14.3
Pressure on common duct by nodes	8	57.2
Infiltration of hepatic duct by Hodgkin's disease	1	7.1
Pressure on hepatic duct	2	14.3
Pressure and infiltration of com- mon duct and hepatic duct	1	7.1

^{*} The bile duct involvement did not cause dilatation of the bile ducts above the lesion.

(70.1 per cent) Hodgkin's disease was present, passive congestion was noted in ten cases (17.6 per cent), hemosiderosis in nine (15.8 per cent), infarction in four (7.1 per cent), myeloid metaplasia in three (5.3 per cent), fibrosis in one (1.8 per cent) and amyloid in one (1.8 per cent). The spleen was absent due to previous surgical removal in one case (1.8 per cent). Infarction and Hodgkin's disease were present in three cases (5.3 per cent). The weight of the spleen as determined at autopsy varied from 60 to 1,900 gm. (mean weight 500 gm.).

The pancreas was found to be normal in thirty-three cases (58 per cent); it was infiltrated with Hodgkin's disease in thirteen cases (22.8 per cent); and other changes, such as chronic pancreatitis and fibrosis, were found in eleven cases (19.2 per cent). The portal vein was thrombosed in three cases (5.3 per cent). Lymph nodes in the portal area were involved with Hodgkin's disease in thirty-seven cases (65 per cent). The gastrointestinal tract was involved with Hodgkin's disease in fifteen cases (26.4 per cent). The locations of the lesions were as follows: stomach, seven cases (46.6 per cent); small bowel, three cases (20 per cent); colon, three cases (20 per cent); multiple areas, two cases (13.4 per cent).

The duration of disease varied from four to 180 months, the mean being thirty-two months. No statistically significant difference in survival was found between males and females. The duration of disease from diagnosis to death varied from four to 180 months, the mean being twenty-three months.

TABLE XII

PATHOLOGIC CHANGES OF LIVER OTHER THAN THOSE DIRECTLY DUE TO TUMOR IN FIFTY-SEVEN JAUNDICED PATIENTS WITH HODGKIN'S DISEASE WHO CAME TO NECROPSY*

11200131		
Pathologic Findings	No. of Patients	Per cent of Total
Passive congestion	20	35.1
Fatty metamorphosis	12	28.1
Hemosiderosis	9	15.8
Portal fibrosis	3	5.3
Bacterial infections	3	5.3
Atrophy of liver cells	3	5.3
Centrilobular necrosis due to		
congestion	2	3.5
Viral hepatitis	2	3.5
Cholelithiasis	2	3.5
Hemangiomas	2	3.5
Fungus infection (Nocardia ab-		
scesses)	1	1.8
Chronic hepatitis	1	1.8
Toxic hepatitis	1	1.8
Chronic cholangitis	1	1.8
Choledocholithiasis (bile ducts		
above the obstruction were		
dilated)	1	1.8
Focal fibrosis	1	1.8
Lymphangiomas	1	1.8
Cloudy swelling	1	1.8
Hepatic cell edema	1	1.8
Bile stasis	1	1.8
Extramedullary hematopoiesis	1	1.8
Portal cirrhosis	1	1.8

^{*} Many patients had multiple findings in the liver.

Fifty-four patients of this series died of Hodgkin's disease (94.6 per cent) or its complications. In two cases (3.5 per cent) the direct cause of death was infection; nocardia septicemia with multiple abscesses in one case and Clostridium welchii septicemia in the other. In one case the cause of death was hepatic coma. In this patient the diagnosis was toxic hepatitis with early cirrhotic changes and severe fatty metamorphosis of the liver, changes ascribed to phenylbutazone therapy. At necropsy, this patient was found to have Hodgkin's disease limited to the para-aortic lymph nodes. In four cases of this series (7 per cent) gastrointestinal hemorrhage was the terminal event. All patients had melena and in two of these hematemesis also occurred. In two of these four patients, the bleeding source was established at necropsy and was Hodgkin's disease of the stomach; in one case the source was a duodenal ulcer. The source was not established in the

TABLE XIII
HOSPHATASE LEVELS IN JAUN

SERUM ALKALINE PHOSPHATASE LEVELS IN JAUNDICED PATIENTS WITH HODGKIN'S DISEASE WITHOUT EVIDENCE OF BONE DISEASE

Serum Alkaline Phosphatase (Bodansky units)	No Hodgkin's Disease in Liver or Extra- hepatic Bile Duct	Hodgkin's Disease in Liver, with or without Extra- hepatic Bile Duct Obstruction	Per cent of Total	
	No. of Patients	No. of Patients		
Below 10 units	9	10	30	
Above 10 units	0	23	70	
Total	9	33	100	

remaining case, a patient who had uremia and thrombocytopenia.

Correlation Between the Clinical and Laboratory Findings and the Pathogenesis of Jaundice. Correlation of the clinical signs and symptoms and the results of laboratory examinations with the pathologic findings was attempted to determine whether or not obstructive jaundice directly related to the underlying Hodgkin's disease could be distinguished from jaundice due to other causes.

In the absence of bone disease, the serum alkaline phosphatase was found to be of help in differentiating between patients without Hodgkin's disease in the liver and patients with bile duct obstruction and/or liver involvement. Nine patients without Hodgkin's disease in the liver all gave values less than 10 Bodansky units whereas 69.6 per cent of the patients with Hodgkin's disease in the liver and/or extrahepatic biliary tract with obstruction gave values of 10 or more Bodansky units. (Table XIII.) This difference is significant in the 5 per cent range (p = < 0.05). In two patients in whom jaundice was caused by extrahepatic biliary obstruction the serum alkaline phosphatase was 17.1 and 27.2 Bodansky units, respectively.

A thymol turbidity test was performed in thirty patients with Hodgkin's disease involving the liver with or without existing partial extrahepatic bile duct obstruction. In fifteen it was

normal (up to 1.8 units in our laboratory); in fifteen it was positive. The highest value in this group was 8 units, the mean value being 4.35 units. In the three patients with hepatitis in our series the values ranged from 3.8 to 10.25 units. In the test patients with other abnormalities in the liver, the values did not exceed 4 units. Thus it would seem that a marked elevation of thymol turbidity, to levels of 10 units, would favor hepatitis rather than Hodgkin's disease of the liver as the cause of jaundice in such patients. However, these differences are not significant statistically.

The following laboratory tests were found to be of no definite help in establishing the mechanism of jaundice in these cases: hemogram, serum bilirubin level (direct and indirect), cephalin flocculation, total serum protein, albumin and globulin, total cholesterol, direct and indirect antiglobulin (Coombs' test), prothrombin time, bromosulfalein retention. The total serum cholesterol was over 200 mg. per cent in three of the five patients with extrahepatic bile duct obstruction in whom this test was performed. In none of the fourteen patients without bile duct obstruction, in whom cholesterol levels were determined, did the level exceed 200 mg. per cent.

The SGO-T level was not determined serially in an adequate number of autopsy cases in order to enable us to evaluate its significance in this series; however, in three cases of hepatitis high values were found.

We found no clinical sign or symptom that would help to determine with confidence whether we are dealing with Hodgkin's disease of the liver, extrahepatic bile duct obstruction, both, or some other cause of jaundice.

COMMENTS

In only two cases of our autopsy series (3.5 per cent) was extrahepatic bile duct obstruction demonstrated as the sole cause of jaundice, findings in agreement with Beatty's observations [34]. This mechanism, then, is rare as the sole cause of jaundice in Hodgkin's disease. Partial extrahepatic bile duct obstruction in conjunction with Hodgkin's disease of the liver was found in fourteen of our cases (24.6 per cent). The obstruction, however, most probably was not the cause of jaundice in these cases since no bile duct dilatation above the lesion was found.

Liver involvement with Hodgkin's disease was the most common mechanism of jaundice

in our autopsy series, occurring in forty patients (70.2 per cent). In all these patients substantial additional pathologic changes of the liver (such as passive congestion, fatty infiltration, hemosiderosis) were found but these could not of themselves explain the jaundice in most cases; however, they may have been contributory factors.

A substantial portion of the patients in our autopsy series (fifteen patients, 26.3 per cent) did not have either extraphepatic biliary tract obstruction or intrahepatic Hodgkin's disease. However, in only a few of the patients, namely, those with hepatitis (two cases), cirrhosis (one case) and choledocholithiasis (one case), can the findings explain the presence of jaundice. Since hemolytic anemia was proved clinically in only three of the remaining cases, a satisfactory explanation for jaundice was not at hand in 14 per cent of the cases in the autopsy series.

It is important to diagnose correctly the cause of jaundice in patients with Hodgkin's disease since this may be a factor in the choice of therapy. However, in our experience the clinical findings and the conventional liver function tests were not very helpful in establishing the cause of jaundice. The serum alkaline phosphatase, in the absence of bone disease, was found to be of aid in distinguishing between Hodgkin's involvement of the liver, with or without bile duct obstruction, when the value exceeded 10 Bodansky units. However, ten of thirty-three patients (30 per cent) with Hodgkin's involvement of the liver, with or without bile duct obstruction, had values below 10 Bodansky units. Bone disease, as determined roentgenographically, was present in 3.4 per cent of the total series of 116 patients with jaundice who were studied; in these cases one cannot use the alkaline phosphatase as an index of liver function.

There was significant bromsulfalein retention in all cases of Hodgkin's disease with jaundice in which this test was made, hence it did not help to establish the mechanism of jaundice.

Serial determinations of SGO-T help to establish the diagnosis of hepatitis, as in three cases of our series. Determinations of other serum enzymes, such as lactic dehydrogenase, isocitric dehydrogenase, malic dehydrogenase, phosphohexoisomerase, aldolase, leucine aminopeptidase, and of serum vitamin B₁₂ levels were not made in our cases. However, from the data

reported by others [39,40-44,70-77] it would seem worthwhile to evaluate the significance of these tests in the jaundiced patient with Hodgkin's disease.

Liver biopsy was performed in only six cases (5.16 per cent of the total series) and proved helpful in these instances. No mortality or morbidity resulted from this procedure. One must take into account the fact that 27.6 per cent of the patients in the whole series had a platelet count below 100,000 per cu. mm., thus interdicting liver aspiration biopsy. The prothrombin times were prolonged in all patients so tested in this series. In some instances, this defect was corrected after the administration of vitamin K.

Although hemolytic anemia was not very common (6.8 per cent of the whole series), it caused jaundice more often in this series than extrahepatic biliary tract obstruction. The serum total bilirubin in the jaundiced patients with proved hemolysis varied from 1.6 to 6.2 mg. per cent, the median being 5.1 mg. per cent.

In our series, regression of jaundice occurred in 12 per cent of the seventy-five patients in whom therapeutic evaluation was possible. Thus it would seem that therapeutic efforts are justified. One would expect the most gratifying effects of therapy in cases in which the underlying cause of jaundice is not Hodgkin's disease per se, such as viral and toxic hepatitis, cirrhosis, choledocholithiasis. Therapy of such conditions should be similar in the patient with Hodgkin's disease as in patients without Hodgkin's disease.

To the best of our knowledge the influence of ionizing radiation on the course of hepatitis and other non-neoplastic liver disease is not established. Experimental work with healthy animals [67] and studies with cancer patients [68,69] indicate that the liver epithelial cells are quite radioresistant. However, until further data on the influence of ionizing radiation on nonneoplastic liver disease are available, such therapy must be considered to be detrimental. Therefore radiotherapy to the liver should not be prescribed nor should radiomimetic chemotherapeutic agents be administered to the jaundiced patient with Hodgkin's disease in an attempt to alleviate this symptom, before every effort has been made to establish the cause of jaundice. If there is strong diagnostic evidence to suggest extrahepatic bile duct obstruction by tumor, radiotherapy directed to the porta

hepatis would appear to be justified as a therapeutic test. In such an event the amount of radiation to the liver should be kept at a minimum. Good results can be obtained in extrahepatic bile duct obstruction due to lymphoma. Hemolytic jaundice should be managed with steroid therapy or radiation to the spleen in the presence of splenomegaly. In selected cases splenectomy may be considered.

In the cases in which the underlying cause of jaundice is tumor involvement of the liver the therapeutic outlook at present appears to be less encouraging. In this situation radiotherapy to the liver, with or without chemotherapy, may be indicated. Such therapy, if successful, would result in fibrosis of the tumor tissue. The effects of such a process on the liver would depend upon the degree of resulting fibrosis.

It will be noted that the incidence of jaundice in our present series of patients with Hodgkin's disease was higher (13.3 per cent) than that reported in the literature (3 to 8 per cent). If we consider, however, the incidence of jaundice in the living patients versus the incidence of jaundice in the deceased patients, the incidence in our living group was 3.8 per cent, a figure that is in agreement with the data reported in the literature.

In 35.9 per cent of the patients in this series the jaundice was mild (less than 3 mg. per cent total bilirubin). The three patients with viral hepatitis and the two patients with extrahepatic bile duct obstruction showed higher values of serum bilirubin. The median duration of jaundice in our cases was two weeks. The occurrence of jaundice was an ominous prognostic sign in most of the cases, since in 89.7 per cent of the cases it was a terminal or preterminal event.

Pruritus was present in 41.4 per cent of the cases in this series. It is difficult to decide if this symptom was caused by the jaundice, by the Hodgkin's disease, or by both. It occurred in patients with and without extrahepatic bile duct obstruction and therefore is not of great help in diagnosing the cause of jaundice. Ascites was present in 30.1 per cent of the whole series, and peripheral edema was found in 26.7 per cent; in 12.9 per cent of the cases both were present. In only two patients with ascites (5.7 per cent) was the serum albumin level below 1 gm. per cent; and in only one patient with peripheral edema (3.2 per cent) was the serum albumin below 1 gm. per cent. In all other cases,

the serum albumin was within normal limits. In the autopsy series, thrombosis of the inferior vena cava was found in three patients with peripheral edema and ascites; thrombosis of the portal and splenic veins was found in one case. In two patients with thrombosis of the inferior vena cava the iliac veins were thrombosed as well. All these patients had normal serum albumin levels. Renal causes of peripheral edema also were found in our series; for example, a case of lower nephron nephrosis following an incompatible blood transfusion and a case of acute glomerulonephritis. Congestive heart failure was the cause of peripheral edema in one patient with rheumatic mitral valvular disease. In the rest of the patients, we could not explain satisfactorily the mechanisms involved in the production of peripheral edema, ascites, or both. It is conceivable that the retroperitoneal nodes present in many of our patients embarrassed the venous circulation, and thus contributed to the development of the peripheral edema.

It is of interest to note that 11.3 per cent of the 116 patients who were studied did not have either a palpable liver or a palpable spleen at any stage of their disease. The liver alone was not palpable in 13.8 per cent of the cases, and the spleen alone was not palpable in 37.9 per cent of the cases. However, in the autopsy group there was no good correlation between the size of the liver or spleen during life as compared to weight at necropsy, nor was there a good correlation between the size of the organs during life as compared to the pathologic findings at autopsy.

Our autopsy material shows that Hodgkin's tumor, regardless of its histologic type, can impinge upon the common bile duct, intrahepatic bile ducts or both, either by pressure, infiltration, or both. The tumor also invaded the portal vein in one case, causing thrombosis of the portal vein. In an additional two cases, portal vein thrombosis was present without tumor invasion. Lymph node involvement in the portal area was observed in 65 per cent of the autopsy series so that one would expect a higher incidence of extrahepatic bile duct obstruction than was observed.

SUMMARY

The pertinent literature dealing with jaundice in Hodgkin's disease is reviewed, and an analysis is made of a series of 116 cases of jaundiced patients with Hodgkin's disease observed at the Memorial Center. The pertinent pathologic findings in fifty-seven patients who came to autopsy also are presented.

Evaluation of the cause of jaundice in Hodgkin's disease often is difficult. The chief cause of jaundice in our autopsy series was, in order of frequency, liver involvement with Hodgkin's disease (70.2 per cent), no satisfactory pathologic or clinical explanation of jaundice (14 per cent), hemolytic anemia (5.2 per cent), extrahepatic bile duct obstruction due to tumor (3.5 per cent), hepatitis (3.5 per cent), choledocholithiasis (1.8 per cent), cirrhosis (1.8 per cent).

The conventional liver function tests were not very helpful in establishing the cause of jaundice. Liver biopsy, whenever feasible and not contraindicated by the danger of hemorrhage, should be used more extensively in order to establish the cause of jaundice.

Some therapeutic considerations in the jaundiced patient with Hodgkin's disease are discussed.

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Parathyroid Hormone*

Nature and Mechanism of Action

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THE past five years have seen a resurgence of interest in the study of the parathyroid glands and the parathyroid hormone. The introduction of new and better assay methods by Munson in 1955 [1] and Davies, Mussett and Gordon in 1954 [2] led to fresh attempts to purify further the then existing crude parathyroid extracts. Within the past year those purification studies have led to isolation of the parathyroid hormone [3-6]. As a natural corollary to the purification studies, renewed efforts have been made to resolve the problems of parathyroid physiology and to initiate studies on the biochemical effects of the hormone. It is the purpose of this review to summarize the results of this recent work and to present an hypothesis concerning the mechanism of action of the parathyroid hormone.

NATURE OF THE PARATHYROID HORMONE

The first stable crude parathyroid extracts were obtained by Collip in 1925 by extracting bovine glands with hot dilute hydrochloric acid [7]. Final purification of the active principle from such extracts has recently been achieved [4]. The active principle is a polypeptide or protein having a molecular weight varying between 3,800 and 5,200, depending upon the initial conditions of acid extraction [4].

In 1959 Aurbach [8] developed a method for the extraction of the active principle using aqueous phenol solutions. Using Aurbach's extraction method, Rasmussen and Craig [5] have recently isolated and characterized a single protein with a molecular weight of approximately 9,500 which is homogeneous by countercurrent distribution, paper and column chromatography, and ultracentrifugation; contains no cystine; and possesses a single end terminal amino acid, alanine. A comparison of the amino acid composition of this protein with that of the smaller active polypeptides obtained by acid extraction indicates that the smaller polypeptides are undoubtedly fragments of the larger phenol-extracted protein. Thus the present evidence indicates that bovine parathyroid hormone is a protein with a molecular weight of approximately 9,500, consisting of a single polypeptide chain which can be partially hydrolysed without complete loss of biologic activity.

It is of particular interest that the purest hormone preparations available contain both calcium-mobilizing and phosphaturic activity.

MECHANISM OF ACTION OF THE PARATHYROID HORMONE

The control of the concentration of calcium in the plasma and extracellular fluid appears to be one of the most closely regulated homeostatic mechanisms in the body. Ever since MacCallum and Voegtlin's classic work [9] it has been known that the parathyroid glands play an important role in this mechanism. However, since the early 1930's a controversy has existed concerning the mechanism of action of the parathyroid hormone. On the one hand there have been those who favor the view that the primary action of this hormone is upon the renal excretion of phosphate; the changes in the concentration of calcium in the plasma and the mobilization of calcium from bone being considered to be a consequence of this renal effect. On the other hand, a number of investigators have considered that the primary effect of the hormone is upon the resorption of bone,

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the renal and other effects being secondary [10]. In fact, it has even been suggested that the phosphaturic action of parathyroid extracts is due to non-specific proteins present in such extracts.

The various arguments for and against the conflicting theories have been summarized [11,12] and need not be repeated here.

RELATIONSHIP BETWEEN IONS IN SOLUTION AND BONE MATERIAL

Before turning to a consideration of the mechanism of action of parathyroid hormone, it is essential to summarize briefly some of the present concepts concerning the structure of the bone mineral and its relationship to the calcium and phosphate in plasma and extracellular fluid. The complexity of this latter relationship is such that any understanding of it in precise physicochemical terms is impossible, primarily because methods are not available currently for determination of the chemical activities of the various ion species (Ca++, HPO₄-, H₂PO₄-, PO₄-, OH-, Mg⁺⁺, Na⁺). It would indeed be most helpful if such activities could be directly measured. However they can be estimated only in a very roundabout fashion involving a number of assumptions which may not hold in a complex solution such as the extracellular fluid (ECF). Neuman and Neuman in their recent book have introduced these concepts into this field [13] but have not made sufficiently clear the numerous assumptions involved. Conceptually, one would like to consider the problem in these terms and in the ensuing discussion the calcium ion activity (Aca++) and phosphate ion activity (AHPO4-) of ECF (as represented by the species HPO₄=) will be considered as existing in equilibrium with the hydroxyapatite crystals (A_{Ca}⁺⁺ · A_{HPO4}⁻ = hydroxyapatite). However, this equilibrium cannot be considered as simple as the one proposed by Neuman and Neuman (Ca⁺⁺ + HPO₄⁻⁻ = priori reason to assume that in vivo a secondary calcium phosphate is the initial product of calcification, which then hydrolyses to the hydroxyapatite. Actually, as pointed out by Glimcher [14], in all likelihood the initial product is the hydroxyapatite crystal and furthermore its formation is induced by the interaction of specific sites on the organic matrix of bone (collagen) with the ambient ions. This being so, any precise formulation of this process must consider the specific orienting or binding sites

in the bone matrix. In addition, Glimcher has stressed the fact that a phase transition takes place when nucleation of apatite crystals occurs. This provides a further difficulty in developing a simple precise formulation of the relationship under discussion. (The interested reader is referred to Glimcher's recent review [14] for a more thorough consideration of this problem.) In the present state of our ignorance the best we can do is to recognize that there is some very intimate relationship between the circulating ions and bone mineral. From the available biologic information it is apparent that the state of saturation of the bodily fluids is normally such that new bone collagen is readily calcified. Furthermore this state of saturation appears to be maintained regardless of the parathyroid status of the organism, as will be discussed subsequently. Obviously the factors which determine the net removal of calcium and phosphate from the ECF are the amount of calcifiable or partially calcified matrix available to accept it. This process has been called bone deposition (or accretion) and must be clearly distinguished from the process of ion exchange which goes on at a much greater rate [15]. This latter process of ion exchange occurs between the various ions in the crystal surface of the bone mineral and the ions in the ECF. Only certain features of this process are germane to our discussion. The most important are that not all the calcium ions in bone are freely exchangeable; that electroneutrality must be maintained; and that no net exchange of ions can take place. Hence, the only way calcium ions can enter the ECF by such ion exchange process is either for the bone crystal to take up H+, Na+, Mg++ or other cations; or for the ion product (Aca++ · AHPO4=) in the plasma to be lowered by some means. Although this ion exchange process is usually considered to take place directly between the ECF bathing the apatite crystals and the crystal surfaces, there is some question whether or not there is some cellular intermediation in this process because the periosteum and endosteum are highly regular, cellular membranes which must certainly regulate to some extent the exchange of ions between the bone mineral and ECF.

If it is accepted that the bodily fluids are saturated with respect to calcium and phosphate (it is important to bear in mind here that the oversaturation between these ions and bone matrix is only apparent) then, once calcification is initiated, it is legitimate to ask why this process

does not continue indefinitely. In this regard it is well to point out that bone is a complex organ composed of three major components, namely, collagen, ground substance and bone mineral. Recent evidence suggests that much of the bone crystal is located within the hollow collagen fibrils [14]. Here then is a natural barrier to indefinite apatite deposition, for each fibril can take up only a definite quantity of mineral, depending upon its volume. As shown by the work of Deakins [16,17], as calcification proceeds the water content of the mineral phase decreases until a point is reached where the crystal becomes essentially "diffusion-locked," inasmuch as the crystals no longer exchange ions by the process of diffusion in an aqueous medium. This purely physical process leads quite clearly to a cessation of further mineralization.

Thus current theories lead to a picture of calcification as being initiated by specific sites within the collagen fibril; once initiated it continues as a passive process at a progressively slower rate as water is progressively excluded until a point is reached where no further significant exchange takes place between the crystals and the ambient ions. Crystal growth then stops. Obviously, there are other regulatory factors involved in this process, such as the state of the ground substance.

It should be pointed out that the role of the osteoblast appears to be confined to laying down a calcifiable collagen fibril in a suitable ground substance. The factors controlling this osteoblastic activity are poorly understood at present. One of them appears to be mechanical stress upon the bone, but the manner in which this message is translated into a biochemical stimulus is completely unknown. The actual gross dimensions of any bone are normally determined by the rate of bone collagen deposition as controlled by the osteoblasts, and (because of the requirements of bone growth and secondarily the need to maintain the Aca++ of the extracellular fluid relatively constant) the rate of bone resorption, which is also under cellular control. In this latter process the nature of the cell type involved is still being debated, but it is now widely accepted that at least the osteoclasts do play a role. It is the various bone cells and the two processes which they control which determine the final architecture of the bone, and upon which the various vitamins and hormones exert their effect. It has been suggested by Bloom [18] that these various cells have a similar origin and

are converted from osteoblast (i.e., collagendepositing cells) to osteoclasts (i.e., boneresorbing cells) and vice versa under the influence of various agents in their environment. Because there is now good evidence that the parathyroid hormone has a direct effect upon the process of bone resorption, this process will be discussed in some detail.

ROLE OF THE PARATHYROID GLANDS

The primary function of the parathyroid glands, mediated by their secretion of the parathyroid hormone, appears to be maintenance of the concentration of calcium ion activity in the plasma within narrow limits despite wide fluctuations in calcium intake, calcium excretion and bone deposition. Conversely, the secretory function of these glands is controlled by the level of ionized calcium, in physicochemical terms the calcium ion activity (A_{Ca}^{++}) , in the plasma of the organism. From a servomechanical point of view these two regulatory functions constitute a negative feedback mechanism. In analyzing the experimental facts concerning this hypothesis the data naturally fall into two categories, (1) those dealing with the peripheral effects of the hormone, and (2) those dealing with the factors controlling the rate of secretion of the hormone from the gland. The latter data will be considered first.

The Regulation of the Secretory Activity of the Parathyroid Glands. There is no question that a low calcium diet results in hypertrophy and hyperplasia (and therefore presumably increased secretory activity) of the parathyroid glands [11,12,19-21]. On the other hand, high calcium diets have been shown to lead to hypoplasia of the parathyroids. These facts can be interpreted as indicating the primary importance of the concentration of plasma calcium as the factor regulating the secretory activity of these glands.

Unfortunately, there is a large body of information which, while not refuting the hypothesis just stated, is interpreted to indicate that the level of phosphate in the plasma also is important [23,24]. This includes data of two types. When rats are fed diets containing large amounts of a phosphorus-containing compound, parathyroid hyperplasia is usually observed. However, many of the experiments have been poorly controlled because the diets have been low in calcium as well [11]. In a study designed to obviate this difficulty, Stoerk and Carnes [25] used diets in which the total amounts and ratios

of these two elements varied over a wide range. They found that parathyroid enlargement correlated almost perfectly with the serum calcium values of the animals but showed no definite relation to the plasma inorganic

phosphate values.

The other type of data comes from the studies of the effect of pancreatic, anterior pituitary and adrenal dysfunction upon parathyroid activity. Although at one time it was considered that the parathyroids were directly under the control of the anterior pituitary, this has been shown not to be the case. It is well established, however, that some relationship does exist. From the work of Tornblom in rabbits [26] and Engfeldt in rats [27], as well as a great deal of clinical data [28,29], it is apparent that the adrenal and the pancreas, as well as the pituitary, all exert a regulatory effect on the serum phosphate concentration. In the absence of the adrenals, in diabetes and after injection of growth hormone there is an elevation of plasma phosphate. Both Engfeldt and Tornblom observed parathyroid enlargement under these conditions and for this reason came to the conclusion that the level of plasma phosphate had a direct influence upon parathyroid activity. However, Tornblom clearly showed that when the parathyroids were removed and the animals were given hypophyseal extracts there was a fall in plasma calcium as well as a rise in plasma phosphate, whereas injection of hypophyseal extracts into animals with intact parathyroids results in a rise in plasma phosphate without a fall in plasma calcium. Thus the presence of the parathyroids prevents the expected fall in plasma calcium presumably because they are stimulated to increased activity as soon as the level of calcium begins to fall. These observations aid in understanding the reason for the high incidence of parathyroid hyperplasia and adenomas in subjects with acromegaly.

All the data concerning the role of phosphate in stimulating parathyroid activity can be brought into line with the present thesis if it is recognized that any such effect by phosphate is brought about through its effect on plasma calcium. When the plasma phosphate is increased, plasma calcium falls [30,31], and vice versa, i.e., $(A_{Ca}^{++} \cdot A_{HPO_4}^{--} = K)$ regardless of the parathyroid status of the organism. Obviously, this is only a relative constant since in states of vitamin D deficiency this constant does not hold, and K appears to be higher in

young than in old organisms. Supporting evidence comes from several sources. One of the most striking results is the data obtained by Albright et al. [32] in a patient with hyperparathyroidism (presumably having a constant but excessive secretion of hormone). In this patient with hypercalcemia and hypophosphatemia the administration of a high phosphate diet resulted in a rise in the concentration of plasma phosphate and a fall in the concentration of plasma calcium to normal levels. Conversely, the administration of a high calcium, low phosphorus diet is often effective in relieving the tetany of hypoparathyroidism. However, it is not usually possible to bring the plasma values back to normal, primarily because it is not possible to lower the plasma phosphate sufficiently. As pointed out years ago by Shelling [21], the most important difference between the metabolism of calcium and phosphate in patients with hypoparathyroidism and normal subjects is the inability of the hypoparathyroid subject to excrete phosphate. Albright et al. [33] also showed that there was a reciprocal relationship between the concentrations of these two elements in hypoparathyroid subjects given various doses of parathyroid extracts. These data will be discussed subsequently.

Perhaps the most convincing piece of experimental evidence which supports the view that the secretory activity of the parathyroids is regulated by Aca++ comes from the work of Patt and Luckhardt [34]. They found that perfusion of the parathyroids of a dog with calciumfree blood (still containing phosphate) resulted in the production of a calcium-mobilizing factor which was not produced when the gland was

perfused with normal blood.

In summary, it can be stated that, on the basis of the present evidence, it appears that the primary factor regulating the secretory activity of the parathyroid glands is the calcium ion

activity (A_{Ca}⁺⁺) of the plasma.

Peripheral Effects of the Parathyroid Hormone Action on Kikney. The outstanding symptoms following extirpation of the parathyroid glands are those attributed to the increased neural and muscular excitability coincident to the fall in Aca++ in the plasma. The four outstanding metabolic changes are hypocalcemia, hyperphosphatemia, hypocalciuria and hypophosphaturia [28]. These changes are well documented in both man and animals [11]. However, an important finding of Talmage is that initially

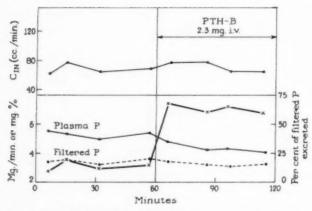


Fig. 1. The changes in inulin clearance (C_{in}), filtered phosphate, plasma phosphate and excreted phosphate in a human hypoparathyroid subject given an intravenous infusion of parathyroid hormone-B.

there is an increased excretion of calcium in the urine of rats following parathyroidectomy. This is followed by a definite decrease of calcium excretion only after the plasma calcium has fallen significantly [35]. This finding suggests that there is a decreased rate of tubular reabsorption of calcium in the hypoparathyroid state. Under such conditions, when the plasma calcium is near normal levels, there is a greater than normal excretion of calcium in the urine, but when the plasma calcium concentration falls the amount of calcium filtered through the renal glomeruli is less and can be nearly completely reabsorbed by the renal tubules in spite of a decreased Tm (transfer maximum) for calcium. This is supported by data obtained after the administration of parathormone. It has been shown by Albright and Ellsworth [28] and more recently by Talmage [35] and Kleeman et al. [37] that the initial effect of the administration of parathormone to a hypoparathyroid animal is a fall in urinary calcium, presumably due to an elevation of the Tm for calcium in the renal tubule. It is only after the plasma calcium becomes elevated that the commonly observed hypercalciuria develops. These observations lead one to the view that in addition to its well established effect upon the renal excretion of phosphate, parathyroid hormone influences the rate of reabsorption of calcium by the renal tubule.

That parathyroid hormone controls the renal excretion of phosphate is a well established fact [11,12,21,28,38]. However, the manner in which it exerts this control has been the subject of a great deal of controversy. Many studies have suggested that it does so by increasing glomerular

filtration rate, while an equal number of reports have stressed the importance of its control over tubular reabsorption or secretion. From the recent work of Jacobs [39] and that of Hiatt and Thompson in man [40,41] it appears that the more significant factor is the control of tubular reabsorption or secretion of phosphate. Rich, Horwith, Thompson and Rasmussen [42] have confirmed these findings in man. They found that following the intravenous infusion of highly purified parathyroid extracts there was a rapid (within ten to fifteen minutes) and sustained increase in the urinary phosphate excretion, with little or no change in glomerular filtration rate. (Fig. 1.) Equally convincing evidence comes from the work of Levinsky and Davidson [43] utilizing chickens. These animals have a renal portal circulation which enables one to infuse a substance into a leg vein and thereby perfuse only the ipsilateral kidney. Furthermore, this venous blood appears to perfuse the tubules but not the glomeruli to any great extent. Utilizing this perfusion technic Levinsky and Davidson demonstrated that the infusion of parathyroid extract into one renal portal system resulted in a unilateral increase in phosphate excretion. The final convincing evidence for the direct action of the hormone on the kidney is afforded by the data of Lavender, Aho, Rasmussen and Pullman [36]. (Fig. 2.) These workers have infused purified parathyroid hormone directly into the renal artery of an anesthetized dog and have observed a unilateral phosphaturia on the infused side without changes in glomerular filtration rate.

Since the chicken shows a net tubular secretion of phosphate even in the absence of parathormone infusion, Levinsky and Davidson were unable to determine whether this increased phosphate excretion was the result of increased tubular secretion or decreased tubular reabsorption. It is well established that phosphate is secreted by the tubules of the aglomerular kidney of certain fish and that phosphate secretion occurs in the frog kidney [45]. The occurrence of a similar tubular secretion of phosphate in the mammalian kidney is suggested by the work of Rappaport et al. [46] in their studies of osmotic diuresis, and by the data of Barclay and co-workers [38,48] studying the excretory pattern of urinary phosphate in human subjects receiving phosphate infusions. In their study of the action of parathyroid hormone in man, Kleeman and Cooke [49] suggested that the

hormone controlled this secretory process. The recent work of Nicholson [50] lends further support to this concept and suggests that the hormone controls the rate of phosphate secretion by the distal tubule. Furthermore, de Verdier [51] has shown an increased turnover of P³² in the phosphoprotein and organic phosphate ester fraction in the renal tissue of animals treated with parathyroid extract, which is more consistent with an increased secretion than decreased reabsorption of phosphate.

Although these actions upon the renal handling of calcium and phosphate are the most striking renal effects which follow the administration of parathyroid hormone, other effects have been observed. During the constant intravenous infusion of purified parathyroid hormone in hypoparathyroid patients Rich et al. [42] found a rapid onset of increased excretion of citrate in the urine, an elevation of urinary pH and an increase in total solute excretion. Perhaps all these changes can be attributed to the increased tubular phosphate secretion, resulting in increased sodium excretion, a de-with a resultant increased citrate excretion. The increased solute excretion is of interest in view of the often suggested diuretic effect of this hormone. Experimental data obtained by Engfeldt et al. [52] in rats show that in experimentally induced hyperparathyroidism the concentrating capacity of the kidney is reduced. The relative importance of this effect remains to be determined, because it is known that hypercalcemia per se has a similar effect.

Actions on Bone. The changes resulting from parathyroidectomy are not entirely due to these renal actions, as shown by the work of Talmage et al. [53] in nephrectomized rats, which show a prompt fall in plasma calcium following parathyroidectomy. Monahan and Freeman [54] have made similar observations in nephrectomized dogs. Also, it has been shown that the rate of turnover of radiocalcium (Ca45) is slower in the hypoparathyroid state [55-57] and more rapid than normal in the hyperparathyroid state [12,55]. This would confirm the old observation that the rate of fracture healing is slower in hypoparathyroid than in normal animals [58]. However, hypoparathyroid rats grow at a normal rate when maintained on a normal stock diet [11,59]. The only histologic change observed in the bones of hypoparathyroid subjects is a decreased number of osteoclasts; mineralization

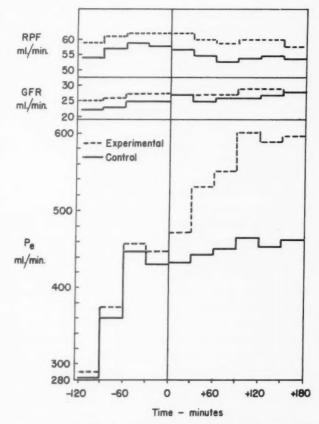


Fig. 2. The changes in renal plasma flow (RPF), glomerular filtration rate (GFR) and phosphate excretion (P₀) following the infusion of parathyroid hormone into the renal artery of a dog. Results from the infused kidney are designated by the broken line (---), those of the other kidney by a solid line (_--). Infusion of hormone was begun at time 0.

is normal [28]. Earlier workers had suggested that demineralization or lack of calcification occurred as a result of parathyroidectomy. Many of these results have been shown to have been the result of dietary rather than hormonal factors.

Engfeldt and Zetterstrom [60] have carried out microradiographic studies on sections of bone obtained from dogs treated with parathyroid hormone, and found that increased bone resorption had occurred, but that the areas of resorption were randomly distributed in both young and old osteons (presumably diffusion-locked). This distribution is similar to that observed in the bone of normal animals [61]. On this basis Engfeldt and Zetterstrom concluded that the primary effect of parathyroid hormone on bone was to increase the rate of the normally occurring resorptive processes.

The first studies which clearly demonstrated a direct effect of parathyroid hormone on bone

were carried out by Barnicot [62]. These were later extended by Chang [63]. Both transplanted parathyroid tissue so as to place it in direct contact with membranous bone of the skull. When such contact was maintained, resportion occurred on the bone surface next to the parathyroid tissue, and bone deposition on the opposite surface. Carrying these procedures further, Gaillard [64a] has demonstrated that parathyroid extract, placed in the culture media of fetal mouse parietal bone grown in tissue culture, caused stimulation of the process of lacunar bone resorption, in the presence of many giant multinuclear osteoclasts. He found that the parathyroid hormone was capable of creating conditions favoring the formation and survival of the osteoclasts, and that the presence of the hormone resulted in the disappearance of typical osteoblasts, which in turn led to a cessation of bone matrix formation. In further work Gaillard [64b] has extended these observations to mouse embryonic limb rudiments in which he has observed that parathyroid extract and, more recently, purified hormone influences the bone, cartilage and connective tissue. The most striking changes were a disappearance of typical osteoblasts, the formation of many multinuclear osteoclasts, dissolution of bone matrix, complex changes in the growth pattern of the epiphyseal cartilage and proliferation of the connective tissue filling the shaft. These changes in the connective tissue and bone observed in vitro are strikingly similar to the changes observed in osteitis fibrosa cystica. The changes in the pattern of cartilage proliferation noted in vitro are of interest in the light of the report of a case of radiologic "rickets" in a child with a parathyroid adenoma [65]; and, as reported many years ago by Shelling [21], the administration of small daily doses of parathyroid extracts to young rats delayed epiphyseal development, resulting in changes which grossly resembled rickets but microscopically the subcartilaginous zone was found to contain much fibrous tissue and many osteoclasts. In these studies Shelling found that the effect of the hormone upon growing rat bones depended upon diet and dose schedule.

If Gaillard's in vitro findings can be considered to reflect the changes occurring in vivo after the administration of parathyroid hormone, one might expect that in short-term experiments there would be a decreased rate of bone growth due to decreased osteoblastic activity, whereas in more prolonged studies compensatory changes

might occur which would result in a new balance between accretion and resorption. It is of interest that Whitehead and Weidman [66] have found a decreased uptake of P³² in all areas of hard tissue in young cats given parathyroid extracts either as a single injection or as multiple injections for a few days. If P³² uptake can be considered a criterion of bone accretion, this would indicate that the predicted decreased rate of bone growth had occurred.

The appearance of the fibrous tissue in the bone of animals with hyperparathyroidism has usually been considered to be a reaction to the osteolytic process. However, Gaillard's results indicate that one of the actions of this hormone is to induce the conversion of osteoblasts to fibroblasts. This point of view has also been suggested by Kroon [67], who proposed that the primary action of the hormone was to induce "redifferentiation" of the osteogenic tissue to argentophil fiber-forming connective tissue, and that this tissue is responsible for the osteolysis.

One change which has often been observed in either spontaneous or experimental hyperparathyroidism is an elevation of the alkaline phosphatase activity of the plasma [68,69]. Less often, an increased acid phosphatase activity has been noted [70,71]. Present concepts about the role of these enzymes are that the alkaline phosphatase activity is an index of osteoblastic activity (but not of the calcification process) whereas acid phosphatase activity is a reflection of the osteolytic process [70-73]. However, Kroon [67] has obtained histochemical evidence showing that increased cellular alkaline phosphatase activity occurs in the fibroblasts of the proliferating connective tissue induced by parathyroid hormone. Hence it would appear that the increased alkaline phosphatase activity in hyperparathyroidism may not indicate osteoblastic activity.

It would seem to be difficult to explain why one does not uniformly encounter signs of bone disease in hyperparathyroid subjects if the effect of the hormone is to induce osteoblasts to become osteoclastic cells. However, if one bears in mind that these cells are subjected to many influences other than the changing levels of parathyroid hormone, it is possible to imagine that under proper conditions increased osteoclastic activity will be followed by a compensatory increase in osteoblastic activity. Actually in marked hyperparathyroidism, in spite of compensatory osteoblastic activity, the osteoclastic

activity predominates, resulting in the decreased bone density observed radiologically and the fractures observed clinically. In other words, the reason for the development of bone weakness and fractures is not due to any abnormality of the calcification mechanism but due to the fact that the predominant cellular activity is osteolysis and such a large percentage of all bone cells are in this state that, despite all the compensatory physiologic adjustments, osteoblastic activity is insufficient to maintain the normal balance between accretion and resorption.

In less severe cases it seems likely that the initially increased osteolysis leads to compensatory increased osteoblastic activity with a resulting increased rate of bone turnover. This being the case it is misleading to classify hyperparathyroidism as occurring with or without bone disease. Changes in bone metabolism undoubtedly occur in all cases of the disease. However, the generally used indices of such changes are so gross that only in moderately severe or longstanding cases of hyperparathyroidism are abnormalities recorded. Also in view of the facts (1) that the availability of phosphate is an important factor in the rate of deposition of bone matrix, and (2) that the calcium:phosphorus ratio in the diet will influence the levels of Aca++ and AHPO4 in the plasma of hyperparathyroid subjects (and therefore influences the supply of phosphate available for bone matrix formation), it is important to point out the role which diet may play in the rate of progression of the signs of bone disease.

In addition to inducing the changes already noted, the administration of parathyroid hormone has been found to cause changes in the staining properties of the ground substance of the bone matrix [74,75]. These changes are considered to be due to a depolymerization of the mucopolysaccharide components, resulting in solubilization and release of bone salts [74,75]. Unfortunately such an interpretation is probably much too simple, as discussed by Glimcher [14]. The changes in staining properties are observed in areas of active bone deposition as well as in areas of bone resorption. On the basis of certain in vitro results Glimcher postulates that depolymerization of these high molecular weight anionic compounds may actually facilitate mineralization of the collagen fibrils. At present all that we can conclude is that in both the process of bone deposition and that of bone resorption, changes occur in the state of aggregation of the high molecular weight polysaccharide components of the ground substance of ossified tissue. From the available evidence it is not possible to conclude that the primary action of parathyroid hormone is to cause depolymerization of this ground substance [74,75], particularly if by this is meant a direct action of the hormone upon these compounds without cellular intermediation. However, it does seem to be well established that this hormone stimulates the process of bone resorption.

The resorption of bone, both of matrix and of inorganic salt, will obviously result in an increased calcium content of the extracellular fluid. However, in the ion exchange process no net increase in calcium can occur unless the calcium ions in the hydration shell or crystal surface are replaced by other cations, including H+, or unless the ion product in plasma (A_{Ca}⁺⁺ · A_{HPO₄}⁼) decreases, in which case both calcium and phosphate leave the bone. Because no striking changes in plasma pH or cation concentrations other than Ca++ occur following the administration of parathyroid hormone, it seems unlikely that the hormone acts by influencing ion exchange reactions between the crystal surfaces and the extracellular fluid (other than through its action of decreasing plasma A_{HPO4} by increasing the urinary excretion of phosphate). This is borne out by abundant histologic and pathologic data which demonstrated that the loss of both bone salts and matrix is involved in the resorption process stimulated by parathyroid hormone [42,76-78]. There are also data from radioisotope work which clearly show that the parathyroid hormone will mobilize Ca45 from the skeleton seventy-five or more days after the administration of isotope, at a time when practically none of the isotope is in the readily exchangeable compartments [79-81] whereas, as Talmage and Elliot [82] have shown, parathyroid hormone does not alter the rate of removal of recently exchanged isotope (the isotope taken up by bone in the first eighteen hours after administration of radiocalcium) [82]. It has never been established that this hormone causes loss of bone mineral without simultaneous loss of the organic phase of bone. On the other hand, there is at least one claim that uncalcified bone matrix will undergo resorption under the influence of parathormone

The Neumans [13] have calculated a solubility product, A_{Ca}^{++} times $A_{HPO_4}^{--}$, in the serum of

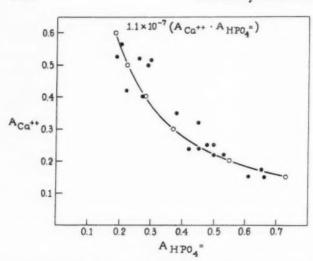


Fig. 3. The reciprocal relationship between A_{Ca}^{++} and A_{BPO4}^{--} in patients with hypoparathyroidism treated with various doses of parathyroid extract. The open circles ($^{\circ}$) represent the theoretic product of 1.1 \times 10⁻⁷, the solid dots ($^{\bullet}$), the experimental values. These data were obtained by recalculating the data recorded by Albright et al. [33].

normal fasting man. Their value was 0.89 X 10⁻⁷, and they have concluded from this that the serum is supersaturated with Ca++ and HPO4= in respect to bone mineral. Neuman and Neuman contend that the parathyroid hormone acts on bone in such a way as to establish an ion gradient between the bone crystal surface and the extracellular fluid so as to maintain the extracellular fluid in the supersaturated state and that "a locally depressed pH prevents the growth of bone crystals at the expense of circulating fluids." As proof of this contention they cite the rapid decline in the product Aca++ · AHPO+ in serum following parathyroid removal or in vitamin D deficiency. They give the figures of 0.6×10^{-7} for the hypoparathyroid state and

 2×10^{-7} for the hyperparathyroid state. From a biologic point of view there is no doubt that deficiency of parathyroid hormone does not lead to the same changes in the capacity of bone to grow and mineralize as does vitamin D deficiency. Actually, if one makes a few re asonable assumptions, similar to those made by the Neumans for arriving at their value for the normal, one can calculate the Aca++ · AHPO4 product in hypo- and hyperparathyroidism as well as in vitamin D deficiency. These calculations are shown in Table 1. The serum values were obtained from actual cases from my personal experience. The striking point about these values is the fact that the product is low only in the case of vitamin D deficiency, a situation in which calcification is not occurring. In both the hypoand hyperparathyroid states this product is normal, due to the reciprocal changes in the concentration of Ca⁺⁺ and HPO₄⁻. This is a point made long ago by Albright et al. [33], and when their data are recalculated using ion activities, rather than concentrations, the points fall reasonably well along the line representing a $(A_{Ca}^{++} \cdot A_{HPO_4}^{-})$ of 1.1 \times 10⁻⁷. (Fig. 3.)

In view of the data recorded in Table 1 and Figure 3, it is difficult to accept the Neuman hypothesis. Rather, it would appear that in animals receiving physiologic amounts of vitamin D, (A_{Ca}⁺⁺·A_{HPO4}⁻) is maintained at a product sufficient to ensure calcification of the organic matrix of bone regardless of the parathyroid status of the organism. (Factors other than vitamin D undoubtedly influence this product; see Appendix.) The influence of the parathyroid hormone would appear to be superimposed upon this basic relationship and would influence the ratio rather than the product of

TABLE I
VARIOUS PARAMETERS OF CALCIUM AND PHOSPHATE IN PLASMA

Physiological Status	Ca		Ca ⁺⁺ Ac	Aca++	Р	HPO ₄ -	Auro =	(Aca++ · AHPO4 ***)
Physiological Status	mg./100 ml.	mM	(mM)	(10-3)	(mg./100 ml.)	(mM)	(10-3)	(10 ⁻⁷)
Normal	10.0	2.5	1.30	0.47	3.1	0.81	0.19	0.89
Hypoparathyroidism	7.5 6.0	1.87	0.90	0.29	6.2	1.63	0.36	1.04
Hyperparathyroidism	14.0 14.0	3.5	2.2	0.79	2.2	0.57	0.13	1.03
Vitamin D deficiency	7.5	1.92	0.95	0.34	2.2	0.57	0.13	0.44

these two ion activities so as to maintain the A_{Ca}^{++} at a level higher than that obtained with physiologic amounts of vitamin D. As already discussed, this is brought about by its actions upon the kidney and gastrointestinal tract (vide infra) as well as on bone. It is obvious that of major importance in controlling this ratio is the action of this hormone upon phosphate excretion.

As pointed out, the administration of parathyroid hormone results in increased osteoclastic activity [76-78]. The most striking structure of this cell is the brush border, first described by Kölliker [84]. Kroon [85] has recently reported a histochemical study of osteoclasts, in bone sections from pigeons given parathyroid hormone, from which he has concluded that this border is formed by cellular projections into the bone substance and that at this border the bone substance is broken down and subsequently liquefied in the vacuoles of the cell. Although this thesis is not universally accepted [86], recent studies with the electron microscope strongly suggest that the "ruffled border" of the osteoclast is a specific structure involved in the resorption of bone, and furthermore, that mineral crystals freed by this resorption are phagocytized and later digested (dissolved) by these cells [87].

The fact remains that parathyroid hormone, through its effect upon the bone cells, increases the rate of bone resorption, a complex process in which the ground substance and collagen fibers are broken down as well as the hydroxyapatite crystals. Practically nothing is known about the way in which the bone cells carry out this complex operation. No satisfactory evidence is yet available to settle whether decalcification precedes the destruction of matrix or not. It is generally considered that the matrix must be demineralized before being broken down [13]. However, as previously discussed, hydroxyapatite crystals in bone are deposited inside the collagen fibrils [14]. This being so, the destruction of bone might well proceed by initial alterations in the organic matrix, as proposed by Hiatt and Shorr [88] and Picard [89], rather than the inorganic elements, as considered by Neuman [13]. The previously mentioned histologic studies of the resorptive process could also be interpreted as favoring the view that the initial changes occur in the matrix.

Although some of the Neumans' proposals can be criticized, their data on the effect of parathyroid hormone upon the production of citrate and lactate in bone seem definite and repro-

ducible. It is particularly interesting that following administration of parathyroid extract the serum citrate rises before the serum calcium [90]. It is entirely possible that, at the localized sites of bone resorption, the parathyroid hormone, through its effect upon acid production by bone cells, does increase the solubility of hydroxyapatite due to the simultaneous increase in citrate ion concentration and decreased pH, as proposed by the Neumans [13,15,16]. The recent work of Elliott and Talmage [91] shows that citrate administered to either nephrectomized or nephrectomized-parathyroidectomized animals mobilized calcium from "deep" areas of bone, suggesting that this ion mobilizes calcium from the same sites as does parathyroid hormone. From these observations it is possible to postulate that the action of parathyroid hormone is to alter the acid production of bone cells and that the resulting changes of pH activate the enzymes responsible for the destruction of the organic matrix of bone. Indeed Cretin [92] has shown by histochemical methods that the pH at the sites of active bone resorption is acid (below pH 7), and Schajowicz and Cabrini [93] have demonstrated large quantities of acid phosphatase at such sites. These observations are of interest in the light of previous work showing that acid phosphatase is related to the osteolytic process [70–73] and its concentration elevated in the plasma in severe cases of hyperparathyroidism [70,71]. Obviously, more data are required before the role of citrate and lactate in this complex process are understood.

A summary of the present concepts of the action of parathyroid hormone on bone is given in Figure 4.

Actions on Other Organs. Following the lead of Albright and Reifenstein [10], most investigators have held that parathyroid hormone has little or no influence upon the intestinal absorption of calcium. However, Aub et al. [94] described a case of hyperparathyroidism in which the fecal calcium excretion (normal before operation at a time when the serum calcium was elevated) rose following removal of a parathyroid adenoma and remained elevated even after the plasma calcium had fallen below normal. Also, Albright et al. [32], in studying a case of hyperparathyroidism, pointed out that their patient had a low fecal calcium at a time when the serum calcium was elevated and suggested that this was brought about by the increased hormonal activity. More direct evidence for this relationship comes from

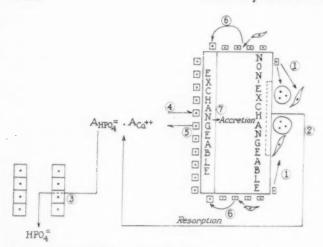


Fig. 4. The primary action of the hormone is to convert potentially osteogenic cells from osteoblastic into osteolytic cells (1), either multinucleated giant cells or an osteolytic fibroblast which elaborates an argentophil fibrous tissue. This results in increased bone resorption (2), possibly by increasing acid production and increasing acid phosphatase activity, resulting in the destruction of both matrix and bone mineral. The release of the latter tends to elevate the level of both ${\rm A_{Ca}}^{++}$ and ${\rm A_{HPO_4}}^{-}$. In addition, the hormone increases distal tubular secretion of phosphate (3), and thereby tends to lower AHPO4 and thus the product Aca++ · AHPO4 . This fall of ion product is buffered by the withdrawal of calcium and phosphate from the exchangeable calcium of bone (4). Since the kidney is more sensitive and responds more rapidly to the hormone, the first effect upon bone is probably action (4). However, as soon as bone resorption is increased (2), and the Aca++ · AHPO4 returned to normal, calcium and phosphate leave the extracellular fluid and return to the exchangeable bone mineral. Thus this compartment serves a buffering function. Although this buffering function superficially appears to be a simple physicochemical process, there is much to suggest that the exchange is controlled by the cellular activity of the osteoblasts [5]. Although the initial effect of the hormone is to decrease osteoblastic activity, the increased bone resorption (2) leads to a weakening of the bone, which leads to mechanical stress and compensatory activation of resting osteogenic cells into active osteoblasts (6), resulting in an increased rate of bone growth and mineral accretion (7). In mild hyperparathyroidism this compensatory change may be sufficient to maintain a nearly normal amount of total bone tissue. However, with more severe degrees of hyperparathyroidism the compensatory increase in osteoblastic activity is insufficient, an imbalance between osteogenesis and osteolysis develops, and the bone density as observed radiologically decreases, leading to the classic picture of hyperparathyroidism with rarefaction of bone and fractures. In this process the trabeculae and certain areas of cortical bone appear to be more sensitive to the action of the hormone and exhibit the pathologic changes sooner and to a greater degree than the major part of cortical bone.

the work of Talmage and Elliott [95]. Working with rats, they found that parathyroidectomy two to four hours before their measurements were

carried out led to a significant decrease (approximately 50 per cent) in the rate of absorption of radiocalcium from an isolated loop of small intestine in vivo. A similar result has been obtained by Rasmussen [96] using isolated sacs of rat small intestine in vivo. In these studies he showed that prior parathyroidectomy led to a decrease in the ability of these sacs to develop and maintain a concentration gradient of calcium between serosal and mucosal fluid.

It has been known for some time that in parathyroidectomized animals and men cataracts develop after a protracted period. This has generally been attributed to a decrease in the content of calcium in bodily fluids and secondarily to a decrease in the calcium content in the lens [10]. However, several investigators report a high calcium content in the lens of parathyroidectomized animals at a time when the calcium concentration of the aqueous humor is lower than normal [97,98], and there has been one claim that the calcium content decreases if such a lens is incubated in vitro with parathyroid extract [99]. If this claim is substantiated, it may be that the lens will be a highly suitable organ for the studying of metabolic effects of parathormone in vitro.

A possible effect of the parathyroids upon lactation is suggested by the work of Folley et al. [100] and that of Munson, Toverud and Kenny [101]. The latter workers obtained data suggesting that the calcium content of milk decreases with increased parathyroid activity induced by low calcium diets given to lactating rats. Parathyroidectomy abolished this reponse.

AN INTEGRATED CONCEPT OF THE MECHANISM OF ACTION OF THE PARATHYROID HORMONE

In considering the sites where the regulation of calcium metabolism could be effected, four naturally come to mind: the bone, kidney, gastrointestinal tract and lactating mammary gland. It is of interest that there is now evidence to suggest that parathyroid hormone influences the calcium exchange at each of these sites. It is important to bear in mind that calcium reabsorption by the renal tubule, calcium absorption from and secretion into the gastrointestinal tract, the deposition and resorption of bone, and the secretion of calcium into the milk continue in the complete absence of the parathyroid glands. Parathyroid hormone, in common with all other mammalian hormones, does not initiate processes de novo but undoubtedly exerts its

influence by controlling the rates of one or more metabolic reactions. In the gastrointestinal tract its primary effect is to increase the rate of absorption of calcium; in the mammary gland it would seem to decrease the rate of calcium secretion; in the kidney it increases tubular calcium reabsorption; and in bone it increases the rate of calcium and phosphorus resorption. All these effects would tend to increase the A_{Ca}⁺⁺ of plasma directly; in addition, the latter effect on bone would tend to increase the A_{HPO₄}, which would in turn tend to decrease A_{Ca}⁺⁺ indirectly, due to their solubility relationship. However, parathormone exerts an additional influence upon the renal tubule, increasing distal tubular phosphate secretion. This results in a fall in AHPO4 which usually more than counterbalances the increased AHPO, resulting from bone dissolution. The net fall in AHPO. indirectly contributes to the elevation of Aca++. (Fig. 5.)

Despite these data, debate on the primary site of action of this hormone continues. In the face of the foregoing evidence a more meaningful question is how the organism integrates these various responses to insure homeostatic control of A_{Ca}⁺⁺ in the blood. Talmage [35] recently proposed an integrated scheme of parathyroid hormone regulation which stresses the importance of these responses. His system has the attributes of a feedback mechanism, a proposal put forward by McLean [102]. However, the latter author considers only a system composed of three elements: bone mineral, Aca++ in plasma, and the parathyroid glands. Neither of these authors has considered the known anatomic and physiologic factors which might place inherent limits upon the various effector organs in this

It has been estimated by Copp [103] that the total bone blood flow of the normal dog is 3 to 7 per cent of the resting cardiac output, in contradistinction to the renal blood flow of 20 to 26 per cent of the cardiac output. Furthermore, as discussed so well by Neuman and Neuman [13], exchange of radioisotopes between blood and the fluid in contact with bone surface is a relatively slow one. For instance, injected deuterium equilibrates with most soft tissues within a few minutes but in bone the exchange is not complete even in four hours (only 90 per cent); the rate of equilibration of Na⁺ is even slower. The Neumans' analogy is that of a river running through a swamp. If this analogy is

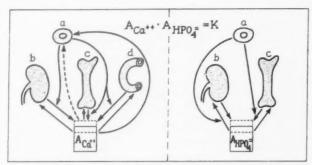


Fig. 5. A schematic representation of parathyroid physiology. A fall in the Aca++ of the plasma stimulates the parathyroid glands (a) to secrete more hormone. The hormone acts upon at least three peripheral tissues, the kidney (b), the bone (c) and the gastrointestinal tract (d). Its effect upon the kidney is to increase the tubular resorption of calcium; upon the bone to increase resorption; and upon the gastrointestinal tract to increase absorption. All these effects tend to elevate directly the A_{Ca}⁺⁺ of plasma, which in turn shuts off the further production of hormone by the gland. In addition, an increased rate of bone resorption leads to an increased release of phosphate into the plasma. However, the hormone has an additional action upon the kidney, that of increasing distal tubular secretion of phosphate. This effect results in a lowering of AHPO4" which usually more than offsets the rise produced by the resorption of bone. The net result is a decrease in AHPO4 which leads to an increase of Aca++, due to their interrelationship $(A_{Ca}^{++} \cdot A_{HPO_4}^{-} \rightleftharpoons K).$

correct, and it is conceded that parathyroid hormone must reach the bone cells in order to exert its effect, then it is very likely that the rate of diffusion of a molecule the size of parathormone through this swamp would be exceedingly slow, and that the rate it reaches the cells in different areas of the bone will depend upon the local blood flow. This system would have an inherent stability, tending to smooth out slight changes in circulating hormone concentration, a buffering-like effect in a sense. It would be slow to respond to larger variations in hormone concentration. The response would build up and decay gradually. On the other hand, the situation in the kidney would be one in which the circulating hormone would reach all the cells nearly simultaneously, and these might be expected to be sensitive to small changes in the concentration of circulating hormone and respond to these changes.

Support for these ideas can be obtained from physiologic data. As pointed out by Davies and Gordon [104], the experiences gained using various assay procedures indicates that larger doses of hormone are required for assays measuring changes in plasma calcium than those using

TABLE II
EFFECT OF PARATHYROID HORMONE

Response	Bone	Kidney	Gastrointestinal Tract
Onset	Slow	Rapid	Intermediate ? Limited
Sensitivity	Insensitive	Sensitive	
Magnitude	Unlimited	Limited	

changes in phosphate excretion. It is well established that with adequate doses of hormone the maximum renal response is obtained in fifteen to forty-five minutes whereas the maximum increase in serum calcium occurs in six or more hours [11,12,42]. Also, when the endogenous production of hormone is stimulated by the infusion of disodium ethylenediamine tetraacetate (EDTA) (this substance binds the calcium in plasma, thereby lowering Aca++) a change in the urinary excretion of phosphorus occurs within twenty minutes [105]. During the prolonged administration of the hormone in adequate doses the serum calcium will continue to increase and eventually cause the death of the organism, but after a certain dosage level of hormone no further effect upon urinary phosphate excretion can be obtained [106,107]. Both renal responses are limited. For it is a fact that despite the increased Tm for calcium, when significant hypercalcemia occurs, hypercalciuria ensues. Likewise there is a maximal response in urinary phosphate excretion produced in a normal animal by an adequate dose of hormone.

If, as McLean postulates, the bone were the only means of regulating the Aca++ of plasma in conjunction with the parathyroids, the resulting feedback system would lead to wide oscillations in the level of A_{Ca}⁺⁺ in the plasma. On the other hand, the kidney is an organ admirably suited, both anatomically and physiologically, to the task of responding rapidly to minor fluctuations of parathyroid concentrations. Thus one can envision negative feedback mechanisms for the regulation of A_{Ca}⁺⁺ involving the parathyroid glands on the one hand, and the bone and the kidney on the other; the renal regulator being rapid to respond, sensitive to small fluctuations in hormone concentration, and of limited capacity; the bone regulator being slow to respond, insensitive, but of nearly unlimited capacity. In such a scheme neither kidney nor bone is considered the primary site of action; both, in their way, contributing to the maintenance of A_{Ca}⁺⁺ of plasma within narrow limits, the integration of the response of these two effector organs giving the organism a greater degree of control than would be the case utilizing either effector alone. (Table II.) This proposal embodies some of the ideas of McLean [102], Neuman and Neuman [13], Howard [107] and Talmage [35], but stresses certain temporal and anatomic factors not previously considered.

The responses of the gastrointestinal tract and other organs have not been included in this discussion primarily because insufficient quantitative data are available. If the data of Talmage and Elliott [95] and those of Rasmussen [96] can be used as an indication, there is a striking change in the rate of calcium absorption from the gut within two hours after parathyroidectomy in the rat. This observation suggests that the organ is more comparable to the kidney than to bone in its response to parathormone. It is obvious that the quantitative importance of any one of these responses to the regulation of the Aca++ of the plasma will depend upon such factors as diet, species and age of the organism, as well as the state of function of the other endocrine glands.

Interpreted in this manner, the data presently available cast considerable doubt on the suggestion that there are two parathyroid hormones, one acting on bone, the other on kidney. This is further borne out by the observations that all the highly purified preparations of parathyroid hormone have both types of biologic activities, and it has not been possible to dissociate them during purification [42].

Of interest to the clinicians is the light that this hypothesis throws on their recent experience with the changing clinical picture of hyperparathyroidism. The older literature stressed the importance of bone involvement, hypercalcemia and hypercalciuria as diagnostic signs. More recently, reports have appeared stressing the fact that perhaps one of the earliest changes is the fall in concentration of inorganic phosphate in the plasma. The diagnosis has even been made in patients with normal concentrations of total plasma calcium, although the ionized (determined by a new chemical method) or diffusible calcium was increased [108]. Also the recent development of diagnostic tests based upon a change in the renal regulation of phosphate excretion is a further indication that more attention is being paid to the changes in phosphate metabolism.

This change in emphasis can be explained by

the fact that, with the increasing interest and knowledge of disorders of calcium metabolism, earlier recognition of hyperparathyroidism has occurred. In view of the present interpretation of the way in which parathyroid hormone acts, it is obvious that the earliest effects of hyperfunction would be manifest in changes in function of the organ most sensitive to its action, i.e., the kidney. Only later in the course of the disease does one see the more striking changes in calcium metabolism and bone histology.

Although we now appear to have a general understanding of the major aspects of parathyroid physiology, many of the details are still obscure, particularly those concerning the process of bone resorption, and those dealing with changes in magnesium metabolism [109-111]. Also ill-defined are the relationship between this endocrine system and the thyroid, pituitary and adrenal systems, all of which are known to influence the metabolism of calcium and phosphate, and thereby undoubtedly the activity of the parathyroid glands. In all likelihood they also condition the responsiveness of the various end organs to the action of parathyroid hormone. Of great interest is the poorly understood relationship between this hormone and the D vitamins. Perhaps the most interesting aspect of this relationship is the possibility that the presence of these vitamins is necessary for the hormone to exert its peripheral effects (permissive action) [112]. We are almost entirely ignorant about the possible etiologic role of these glands in various diseases of abnormal calcification. However, evidence has recently appeared suggesting that they play an important role in the pathogenosis of certain forms of calcific atherosclerosis [113].

At present little is known about the fundamental biochemical effects of the hormone. As has been discussed, there is some evidence that the hormone is involved in the transport of calcium across a variety of membranes (intestinal epithelium, renal tubule, bone cells and mammary epithelium) and that it is involved in the uptake and turnover of phosphate in the kidney and possibly other organs. In addition, the hormone has been shown to increase aerobic lactate production in bone cells in vitro. These data are insufficient to establish any unifying concept as to the mechanism of action of parathyroid hormone on a biochemical level. However, the observation of de Verdier [51] concerning the turnover of radiophosphorus should certainly be investigated further for it may well

be that the fundamental action of the hormone is upon some parameter of phosphate metabolism, and that the effects on calcium transport are secondary to this fundamental action.

APPENDIX

It must be stressed that this formulation, $A_{Ca}^{++} \cdot A_{HPO_4}^{--} = K$, describes what might be called a biologic solubility product, not a physicochemical equilibrium. The product is only a relative constant. The most obvious times when K changes are during the process of growth, and during the state of vitamin D deficiency. In an otherwise normal animal, K does appear to be a constant when the single parameter, parathyroid function, is varied within certain limits. Outside these limits (severe hyperparathyroidism) it would appear that the multiple factors regulating this system break down. Also, in renal disease with secondary hyperparathyroidism there appears, at first glance, to be little constancy in this ion product. However, as pointed out, the estimation of the various ionic activities (A_{Ca}⁺⁺ and A_{HPO4}⁻) even in normal plasma is really an exercise in physicochemical reasoning based on a number of assumptions which may not be completely valid. The application of similar reasoning and assumptions to the calculation of this product in disease is even less meaningful. The recent work of Fanconi and Rose [114] is of interest in this regard. These investigators measured the total, ultrafilterable and ionized calcium in the plasma of human subjects with various disorders of calcium metabolism and have shown that in the alkalosis of hyperventilation the calcium ion concentration changes without change in total calcium concentration. Also in renal disease with azotemia they found a marked increase in the amount of ultrafilterable but non-ionized component of plasma calcium (presumably complexed to organic acids such as citrate and amino acids), but low or normal ionized calcium. The application of this new method of measuring calcium ion concentration in various disease states should certainly aid in our understanding of this problem. However, we still lack any suitable technic for estimating the AHPO, in biologic fluids.

Obviously any acute change in calcium or phosphate metabolism, such as brought about by the infusion of chelating agent or calcium, will not obey this rule of $(A_{Ca}^{++} \cdot A_{HPO_4}^{--} = K)$. These transient states must be differentiated from more prolonged or "steady-state" condi-

tions. Also it is to be expected that this constant may vary somewhat from patient to patient.

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Cushing's Syndrome*

A Study of Fifty Patients

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THE present study of Cushing's syndrome is an analysis of fifty cases, forty-three female and seven male patients who varied in age from eleven months to sixty-eight years. Forty-eight members of the group were white, one was a Negro woman, one a mulatto male. Thirty-two patients were twenty-one to forty years old at the time of onset of the disease. (Table 1.) With the exception of those over fifty years of age and an infant of eleven months, all of whom had adrenal cortical carcinoma, there was little difference in age of onset between the patients with an adrenal tumor, either benign or malignant, and those with non-tumorous adrenal cortical hyperfunction. The frequency with which adrenal carcinoma is the cause of Cushing's syndrome in children has previously been emphasized; twenty-nine such cases have thus far been reported [2]. However, one case of Cushing's syndrome in a child with bilateral adrenal hyperplasia, and one with bilateral adrenal adenomas also have been recorded [2].

Table 1
Age at onset of cushing's syndrome in relation to adrenal pathology

Age at Onset (yr.)	No. of Cases	Carci- noma	Adenoma	Non-tumorous Adrenal Hyperfunction
<1	1	1	0	0
1-10	0	0	0	0
11-20	8	1	0	7
21-30	13	0	3	10
31-40	19	6	5	8
41-50	5	1	0	4
51-60	2	2	0	0
61-70	2	2	0	0

The duration of symptoms of the three groups before admission to the hospital is indicated in Table II. The symptomatology of patients with adrenal carcinoma tends to be more urgent; the succession of symptoms is more rapid, their progression is more hurried, and medical care is usually sought more promptly. However, as with the age of onset, there is considerable overlapping among the three categories.

Histologic examination of one or both adrenal glands was made in forty-five patients (Table III), either after operative removal or at postmortem examination. Twenty-one were found to have an adrenal cortical tumor, of which thirteen were carcinomatous and eight benign. Of the remaining twenty-nine patients, in eleven the adrenals were enlarged, and in thirteen the glands were normal in size, the removed adrenal weighing 5 to 8 gm. In five patients the nature of the adrenal pathology was never established, since they were neither operated upon nor did they succumb to the illness; the fact that the members of this group responded satisfactorily to pituitary radiation would suggest that an

Table II
DURATION OF SYMPTOMS BEFORE FIRST EXAMINATION
IN HOSPITAL IN RELATION TO ADRENAL PATHOLOGY

Dathalam	Pathology No. of Y	Years
rathology	Range	Median
Adrenal carcinoma (13 cases)	<1 to 5	1
Adrenal adenoma (8 cases)	<1 to 8	2
Non-tumorous adrenal hyperfunction (29 cases)		3

^{*} From the Endocrine Laboratory and Clinic of the Department of Medicine, The Mount Sinai Hospital, New York, New York. A prior report [7] dealt more briefly with a smaller series of cases of Cushing's syndrome.
† Aided by a grant from Consiglio Nazionale delle Ricerche (Rome, Italy) in 1958. Present address: Metabolic Unit,
Institute for Occupational Medicine, University of Florence, Italy.

TABLE III
PATHOLOGY OF THE ADRENALS

Pathology	Left Side (no.)	Right Side (no.)	Total No.
Adrenal carcinoma	7	6	13
Adrenal adenoma	3	5	8
Hyperplastic adrenals			11
Normal adrenals *			13
Undetermined		***	5

^{*} Weight of individual glands did not exceed 8 gm.

adrenal cortical tumor was not responsible for the Cushing's syndrome. In ninety-seven autopsy cases collected from the literature and reported by Plotz, Knowlton and Ragan [15], carcinoma of the adrenal was the cause of Cushing's syndrome in sixteen instances, benign tumor in eleven, and non-tumorous adrenal hyperfunction in seventy. Of the latter, hyperplastic adrenals were present in fifty-eight instances.

CLINICAL AND LABORATORY MANIFESTATIONS
OF CUSHING'S SYNDROME

An analysis of the clinical manifestations, both at the onset of the illness and at the time of admission to the hospital (Table IV), revealed no essen-

Table v

COMPARISON OF PERCENTAGE INCIDENCE OF CLINICAL
SIGNS IN MOUNT SINAI HOSPITAL SERIES, PRESBYTERIAN
HOSPITAL SERIES AND CASES COLLECTED FROM
LITERATURE*

Sign	Mount Sinai Series (50 cases)	Columbia Series (33 cases) %	Collected from Literature (189 cases)
Amenorrhea	72	86	71
Obesity	86	97	97
Virilism†	84	73	69
Hypertension	88	84	85
Edema of lower extremities	66	60	28
manifestations.	68	60	23
Plethora	78	89	50
Asthenia	58	83	50

^{*} Presbyterian Hospital series and cases collected from the literature reported by Plotz, Knowlton and Ragan [15].

TABLE IV
PER CENT INCIDENCE OF CLINICAL SIGNS AT TIME OF
ONSET AND AT TIME OF HOSPITAL ADMISSION

Sign	At Time of Onset (%)	At Hospita Admission (%)	
Amenorrhea*	38	72	
Obesity	34	86	
Virilism†	34	84	
Moon facies	22	92	
Oligomenorrhea	17	0	
Menstrual irregularities	0.7	0	
Hypertension	10	88	
Edema of lower extremities	10	66	
Hemorrhagic manifestations.	6	68	
Violaceous striae	6	50	
Diabetes mellitus‡	4	84	
Plethora	0	78	
Asthenia	0	58	
Osteoporosis	0	56	
Pathological fractures	0	40	
Mental disturbances	0	40	
Telengiectasia	0	36	
Cervical fat pad	0	34	

^{*} Of twenty-nine females between sixteen and fortyone years of age.

† Of forty-three females.

tial differences among the groups differing in adrenal pathology. However, considerable differences exist both in the nature of the clinical manifestations and in their incidence with progression of the illness. In Table v is presented a comparison of our data with the report of Plotz, Knowlton and Ragan [17]. The latter included a report on thirty-three patients observed at the Columbia-Presbyterian Medical Center and an additional 189 patients culled from the literature. In the present study the earliest manifestations, in decreasing order of frequency, were: amenorrhea, obesity, virilizing manifestations, moon facies, oligomenorrhea, hypertension, edema of the lower extremities, hemorrhagic manifestations, violaceous striae, diabetes mellitus and menstrual irregularities. Only later did plethora, asthenia, osteoporosis, pathologic fractures, mental disturbances, telangiectasia and a cervical fat pad develop. At some time during the course of the illness fullness of the face, obesity, hypertension, signs of virilism, disturbances in carbohydrate metabolism and plethora developed in most patients. Almost three-fourths of the females within the

[†] Of forty-three females, Mount Sinai Hospital series.

[‡] As manifested by an elevated fasting blood sugar level or a diabetic glucose tolerance curve.

TABLE VI VIRILIZING FEATURES IN THIRTY-SIX FEMALES

Feature					
Increased facial hair	29				
Alopecia	18				
Increased body hair	13				
Acne	13				
Enlarged clitoris	12				
Masculine pubic hair	10				
Masculine voice	51				
Atrophic breasts	4:				

* Eleven of these were less than forty years old.

† These five patients were nineteen, nineteen, thirty-five, thirty-seven and forty-one years old.

These four patients were twenty-three, twenty-five, twenty-eight and thirty-five years old.

relevant age group had amenorrhea. Approximately 70 per cent of the patients had edema of the lower extremities and a similar number exhibited hemorrhagic manifestations. In half or slightly more of the patients asthenia, osteoporosis and violaceous striae developed, 40 per cent or less had pathologic fractures, varying types of mental disturbances, telangiectasia and a cervical fat pad.

Amenorrhea ultimately occurred in 72 per cent of the females between sixteen and forty-one years of age, but as an early manifestation it was present in only one-third of the group. In 17 per cent, oligomenorrhea occurred early, but all subsequently became amenorrheic. Normal menses were maintained throughout the illness in three women, one with adrenal adenoma, the others with Cushing's syndrome due to non-tumorous adrenal cortical hyperfunction. At the time of treatment the three patients had had clinical manifestations of the disorder for slightly less than one year. It is possible that had the disease continued for a longer period amenorrhea may have developed. There is apparently little relationship between the presence of amenorrhea and change in libido. In only onethird of the females between nineteen and fortyfive years of age was libido reduced.

Obesity, including moon facies, was the most common manifestation of the disease and occurred some time during the course of the illness in 92 per cent of the patients and was of the central type in forty, of the diffuse type in three. The remaining seven patients appeared to be of normal build, even slender. The obesity in Cushing's syndrome is more often apparent than

Table VII SEXUAL MANIFESTATIONS IN ADULT MALES (SIX CASES)

Manifestation										
Diminution in libido and/or difficulty in sustaining erection.										
Decreased body hair										
Small and soft testes										
	. 1									
Small penis and prostate										

real. When the body weight of our patients was compared with the average weight of persons of the same age, sex and height it was found that only one-third exceeded the statistical average weight by more than 10 per cent, and in only one-fifth was it in excess of 25 per cent of the normal calculated weight. The appearance of obesity is less frequently due to true adiposity and more often the result of a change in body fat distribution, shortening of the neck and trunk as a result of the osteoporosis and flattening of the vertebral bodies, fullness of the face, and protrusion of the abdomen because of atrophy and laxity of the abdominal musculature. There was no apparent relationship between obesity and the type of adrenal pathology.

Virilism as an early manifestation of Cushing's syndrome occurred in one-third of the patients, but with progression of the disease it was noted in over 80 per cent. The various features of virilism are listed in Table vi. In 16 per cent of the forty-three female patients the clinical signs were those of Cushing's syndrome alone, with no evidence of virilization. Seventy per cent showed minor degrees of virilization, and in 14 per cent the virilizing manifestations were striking. This latter group had marked facial hirsutism, often requiring daily shaving, a male escutcheon, significant enlargement of the clitoris, a bass and husky voice, severe acne and atrophy of the breasts. The incidence of adrenal carcinoma in the patients with marked virilism was somewhat greater than in the other members of the series: Three of the six patients with marked virilization had an adrenal cortical carcinoma, and only 9 per cent of the remaining

All six male patients showed some degree of feminization. (Table VII.) In only one was feminization marked, and this patient had an

thirty-seven females.

Table VIII
SITE OF PATHOLOGIC FRACTURES IN TWENTY CASES

Site										No										
										_		_	_							
Ribs																		*		16
Spinal vertebrae	0				e															11
Pelvic bones																				3
Sternum		*				. ,					×		×	. ,						1
Tibia		*						*		*			×	 	*					1
Metatarsal bones.							. «							 	. *		ė.	*		1

adrenal cortical carcinoma. In the remaining five the adrenals were non-tumorous.

Osteoporosis, as determined by x-ray studies, was present in twenty-eight patients. Twenty had pathologic fractures, most commonly involving the ribs and spine. (Table VIII.) In nine of the sixteen patients with rib fractures, x-ray studies of the chest revealed a characteristic expansion of the anterior ends of the lower ribs proximal to the costochondral junctions, as described by Sussman and Copleman [3]. This abnormality is in all probability due to callus formation secondary to pathologic fracture. Low back pain was present in sixteen patients. The severity of the pain varied considerably, but in four it caused considerable incapacitation. Dorsal kyphosis was noted in twelve patients and was always associated with osteoporosis and vertebral flattening or compression fractures of the dorsal spine. Low back pain also occurred, however, in the absence of any demonstrable evidence of osteoporosis. This symptom was sometimes associated with inability to arise from a sitting position without the use of the upper extremities, suggesting a muscular dystrophy involving the girdle muscles. This is reminiscent of a similar manifestation occasionally encountered with the exogenous administration of adrenal steroids.

Serum calcium determinations were made in thirty-seven patients and in only one was it found to be elevated. The serum inorganic phosphorus was normal in thirty-four of thirty-eight patients and somewhat reduced in the remaining four. The serum alkaline phosphatase was elevated in eleven patients, all of whom had osteoporosis. Normal serum alkaline phosphatase values were found in eleven additional patients with osteoporosis and in twelve without such bone changes. These data would suggest that elevation of the serum alkaline phosphatase implies the presence of osteoporosis, but a nor-

mal value does not exclude the existence of such changes. In two patients we found an increase in the serum alkaline phosphatase prior to roentgenologic demonstration of osteoporosis. In both patients extensive bony changes subsequently developed. Calcium balance studies generally failed to reveal any significant increase in the urinary excretion of calcium [4]. However, the inherent defect in calcium and phosphorus metabolism becomes evident with the administration of corticotropin to patients with Cushing's syndrome, resulting in a pronounced increase in the fecal and urinary excretion of these ions. The negative calcium balance which thus results is due in greater part to fecal loss of calcium and phosphorus [5].

Asthenia and muscular weakness were prominent complaints in over half the patients, and in four the asthenia was so profound as to seriously incapacitate them. In five there was considerable muscular atrophy with particular involvement of the lower extremities. The involved muscles responded promptly and well to faradic stimulation.

Seven patients showed increased susceptibility to skin infections, characterized by recurrent pyoderma, abscess formation and chronic fungus infections. In nineteen cases the skin appeared to be normal. The plethora, violaceous striae atrophica, hemorrhagic manifestations and thinning of the skin are probably due to protein depletion resulting in atrophy of the corium. In addition, there is thinning and dilatation of the arteriolar and venous walls. Both factors contribute to the greater prominence and vulnerability of the subcutaneous blood vessels.

Edema of the lower extremities occurred in thirty-one patients, in the absence of heart failure. It was pitting in character, usually subsided with rest, and responded well to a low sodium intake and the administration of diuretic agents. In two patients, both with adrenal carcinoma, peripheral edema was the most prominent clinical feature, and in one of these Δ_{3,5}-androstadienone-17 was isolated from the urine [6]. After surgical removal of the tumor this steroid disappeared from the urine and the edema subsided, both to recur simultaneously subsequently. In none of the thirty-one members of the group was there any significant decrease in the total serum protein, albumin or globulin values.

Cyanosis was present in two patients with cardiac failure and in five without evidence of

cardiac embarrassment. In this latter group the lips, hands and feet assumed a dusky cyanotic hue resembling acrocyanosis.

The visual fields were studied in thirty-six patients and found to be normal in thirty-five. In one there was a bitemporal constriction and subsequent investigation and operation revealed the presence of a primary chromophobe carcinoma of the pituitary with the typical clinical manifestations of Cushing's syndrome [7]. The sella turcica was enlarged in this patient, but was of normal size and configuration in the remaining forty-nine patients. Some decalcification of the posterior clinoid process and the dorsum sella was seen in those subjects who showed osteoporosis elsewhere. Two female patients with adrenal carcinoma showed marked thickening of the inner table of the frontal bone (hyperostosis frontalis interna), presumably unrelated.

Mental disturbances were exhibited by twenty patients, and included severe depression, paranoid trends, confusion, disorientation, marked emotional lability, euphoria and significant memory defects. Prior to successful treatment most of the subjects were hostile, uncooperative, suspicious and overanxious. Two had overt manic episodes which responded well to electroshock therapy. Electroencephalographic tracings were performed in ten patients, and in eight were recorded as normal. Of the two abnormal tracings, one was interpreted as "diffuse cerebral dysfunction," the other as "diencephalic dysfunction." Headache was a relatively frequent complaint and was present in twenty-three patients. In only three was this symptom referred to as severe. There seemed to be no characteristic pattern to the headache and its duration was quite variable. The blood pressure was elevated in twenty of the twenty-three patients, and those with the more severe headache had the more marked elevations in both the systolic and diastolic pressures. The cerebrospinal fluid was examined in four patients. The cell count, chloride content and colloidal gold curve were normal in all four. The total protein content was increased and varied from 70 to 165 mg. per cent. In two patients with increased blood sugar levels the spinal fluid sugar values also were increased. The cerebrospinal fluid pressure was normal in three patients and elevated to 290 mm. in one.

In five of the thirteen patients with adrenal carcinoma it was possible to palpate an abdomi-

TABLE IX
HEMOGLOBIN, RED BLOOD CELLS AND RETICULOCYTES

Laboratory Data	No. of Cases	Plethora
Hemoglobin (gm./100 ml.)		
10.0-12.0	7	5
12.1-16.0	40	31
16.1-17.4	3	2
Red blood cells (millions/cu. mm.)		
3.5-4.0	3	2
4.1-5.5	30	26
5.6-6.7	8	5
Reticulocytes		
Less than 1 per cent	8	* * *
1.4-3.7 per cent	4	

nal mass in the region of the tumor. The mass was generally deep, firm, non-tender and ill-defined. The corresponding kidney was often displaced inferiorly. In none of the eight patients with an adrenal cortical adenoma could the tumor be palpated.

Ten of the fifty patients had roentgenologically demonstrable cholelithiasis, and ten additional patients had radiopaque renal calculi. This constitutes a considerably higher percentage of calculus formation than is observed in a similar age and sex group of the general population.

Two female patients had had hay fever since childhood. The hay fever disappeared when the first clinical signs of Cushing's syndrome became evident, but reappeared when the Cushing's syndrome was successfully treated.

Hematologic Findings. In Tables IX, x and XI are listed the hematologic studies performed on the patients in this series. The majority had hemoglobin and red blood cell counts which were within the normal range. Seven had a mild normochromic anemia, and in eight the red blood cell count varied from 5.6 to 6.7 million per cu. mm. with a corresponding elevation of the hemoglobin content. The blood volume, employing either Evans blue or Congo red, was determined in five patients. The results were normal in three and elevated in two, both instances of adrenal carcinoma. A plethoric appearance, present in 78 per cent of the group, bore no relationship to either the hemoglobin content or the red blood cell count. Polycythemia, even of a mild degree, was uncommon in our series. The reticulocyte count was slightly elevated in four of twelve patients, and in this

TABLE X
WHITE BLOOD CELLS

Laboratory Data	No. of Cases
White blood cells (per cu. mm.)	
<10,000	24
>10,000	26
Differential count	
Polymorphonuclear leukocytes (per cent)	
<75	17
>75	33
Lymphocytes (per cent)	
<20	32
>20	18
Eosinophils (direct count) (per cu. mm.)	
<100	4
>50	5

group the hemoglobin varied from 13.9 to 15.3 gm. per cent and the red blood cell count from 4.7 to 5.3 millions per cu. mm. Half the patients had a modest increase in the total peripheral white blood cell count, and twothirds had some leukocytosis. Slightly over onethird of the group showed a lymphocytosis. Direct eosinophil counts were made in nine instances and were found to be low. Platelet counts were slightly reduced, varying from 100,000 to 114,000 per cu. mm. in three of twenty-three patients, and the bleeding time was prolonged in one. The prothrombin consumption was impaired in two of nine patients. One, a woman with an adrenal carcinoma, showed, in addition, a prolonged bleeding time. Several weeks after the removal of the tumor the bleeding time became normal and there was some improvement in the prothrombin consumption. Two years later, while the patient

TABLE XII
CARDIOVASCULAR MANIFESTATIONS (FIFTY CASES)

Manifestation							
Hypertension*	44						
Enlargement of the heart	17						
Electrocardiographic evidence of myocardial							
involvement	17						
Eye-ground alterations	25						
Congestive heart failure	2						
Cerebrovascular accidents	2						

^{*} Blood pressure in excess of 150/90 mm. Hg.

TABLE XI
COAGULATION STUDIES

Study	No. Examined	Abnormal
Platelet count	23	3*
Bleeding time	21	1†
Coagulation time	23	0
Clot retraction	14	0
Fibrinolysis	9	0
Prothrombin time	14	0
Prothrombin consumption	9	2‡
Stable factor	9	0
Labile factor	9	0

* Reduced.

† Prolonged.

Impaired.

was still in complete remission, both the bleeding time and the prothrombin consumption were normal. The result of the tourniquet test was positive in seven of twenty-seven patients.

These data suggest that the hemorrhagic manifestations and easy bruisability of Cushing's syndrome are probably not due to any presently demonstrable intrinsic defect of the blood clotting mechanism.

Cardiovascular and Renal Observations. Hypertension was present in forty-four subjects (Table XII) and bore no relationship either to the age of the patient or to the character of the adrenal pathology. This corresponds quite closely to the reported incidence of 85 per cent [15]. The highest blood pressure, 230/130 mm. Hg, was recorded in our youngest patient, an infant less than one year of age with an adrenal carcinoma. Two of the six normotensive patients had an adrenal cortical tumor, and in four the adrenals were non-tumorous. Enlargement of the heart in association with hypertension was present in onethird of the group and an equal number showed electrocardiographic evidence of myocardial damage.

Eye-ground changes were present in half the group. Of these, seventeen showed arteriolar narrowing with or without A-V compression, in three there were exudates and hemorrhages, and in five papilledema. All patients with retinal changes had hypertension. Two women, aged forty-five and forty-six years, sustained cerebrovascular accidents.

Eleven of the fifty subjects had impairment of renal function as determined by urinalysis, the level of the blood urea nitrogen, phenol-

TABLE XIII
RENAL MANIFESTATIONS

Manifestation	No. of Cases
Albuminuria	5 (of 50)
Increased blood urea nitrogen	2 (of 50)
Impaired phenolsulfonphthalein excretion	6 (of 15)
Abnormal urine concentration test	9 (of 22)

sulfonephthalein excretion and urine concentration tests. (Table XIII.) It would seem proper to conclude that the renal changes, like those in the eye grounds and the heart, were secondary to the hypertension rather than to a more specific organ effect of the disease.

Serum Electrolyte Changes. The serum sodium concentration was elevated in thirteen of thirtyeight patients (Table xiv), varying from 146 to 158.2 mEq. per L. The serum chlorides were reduced in six (lowest value, 82 mEq. per L.), the serum potassium was elevated in five and reduced in four patients (as high as 7.6 and as low as 2.5 mEq. per L.). The most frequently encountered abnormality was an increase in the CO₂ content of the blood, up to 42 mEq. per L. in one instance. In only one instance was a "typical" hypochloremic hypopotassemic alkalosis found. In this patient the serum values of the blood electrolytes were: sodium 142.3 mEq. per L., chlorides 82.1 mEq. per L., potassium 2.8 mEq. per L., and CO₂ 42 mEq. per L. Of a total of 138 serum electrolyte determinations, normal values were obtained in eighty-six. There was no demonstrable relationship between the presence of serum electrolyte changes and the character of the adrenal pathology.

The serum calcium concentration was slightly elevated in one patient and reduced in another, the phosphorus was somewhat decreased in four. Hypercholesterolemia was present in twenty-two of thirty-four patients, the highest value being 665 mg. per cent. The increase was not always associated with a lowered basal metabolic rate, since the latter occurred in only one-third of the group. The total proteins varied from 6 to 7.6 gm. per cent in twenty-six patients and were slightly reduced, to 5.3 to 5.9 gm. per cent, in six.

Thyroid Function in Cushing's Syndrome. The thyroid gland was readily palpable in eight patients. In four the gland was diffusely en-

TABLE XIV SERUM ELECTROLYTES

	No. Examined	Normal	Ele- vated	De- creased
Sodium	38	25	13	0
Chloride	40	34	0	6
Potassium	28	19	5	4
CO ₂ content	32	8	24	0
Calcium	27	35	1	1
Phosphorus	38	34	0	4

larged, in four a non-toxic nodular goiter was present. The basal metabolic rate was within the normal range in all eight patients. In one patient with diffuse goiter an adrenal carcinoma was present. Of the four patients with nodular goiters, an adrenal carcinoma was present in one and an adrenal adenoma in two others. Mild exophthalmos was noted in fourteen patients. The basal metabolic rates of this group were either within the normal range or somewhat lowered. Twelve had non-tumorous adrenal cortical hyperfunction and two had an adrenal cortical carcinoma.

The basal metabolic rate was determined on one or more occasions in forty-two patients. In 55 per cent this value varied from plus 15 to minus 15 per cent and in approximately onethird the values fell between minus 15 and minus 36 per cent. Despite the considerable increase in the basal metabolic rate in some patients, and equally marked lowering in several others, none of the group presented clear clinical evidence of either hyper- or hypothyroidism. Of the seven patients in whom elevation of the basal metabolic rate was present, five had an adrenal tumor, either benign or malignant; while of the eighteen patients with a low rate, twelve had no adrenal tumor and the remaining six had an adrenal adenoma. Tracer studies with I131 were made in six subjects and the uptake at the end of twenty-four hours was found to be within the normal range in all. The basal metabolic rate was within normal limits in three and reduced in three. The protein-bound iodine was determined in seven patients, and varied from 3.6 to 5.2 γ per cent in six, and was 9.6 and 9.5 γ per cent in the seventh. The latter had a normal basal metabolic rate and no history could be elicited of prior administration of iodine in connection with x-ray studies of the gallbladder or intravenous pyelography.

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TABLE XV
EXCRETION OF URINARY 17-KETOSTEROIDS

Patients with	No.	Urinary Excretion Increased*	Range (mg./ 24 br. volume)
Excretion of Uris	агу 17-	Ketosteroids	
Adrenocortical carcinoma	9	6	4.0-326
Adrenocortical adenoma Non-tumorous adrenocortical hy-	6	2	4.2- 20.9
perfunction	31	15	2.4- 47.4
Excretion of Urinary	17-Оху	genated Steroids	
Adrenocortical carcinoma	7	7	
Adrenocortical adenoma Non-tumorous adrenocortical hy-	7 2	2	
perfunction	13	13	
Excretion of Urinary 1	7-Hydro	axycorticosteroids	
Adrenocortical carcinoma	1	1	
Adrenocortical adenoma Non-tumorous adrenocortical hy-	1	1	
perfunction	6	6	

^{*}In the first group urinary excretion was more than 17 mg. per twenty-four hours in females and more than 20 mg. per twenty-four hours in males. In the second group it was more than 2 mg. per twenty-four hours, and in the third group more than 11 mg. per twenty-four hours.

Carbohydrate Metabolism. Laboratory evidence of disturbance in carbohydrate metabolism was present in forty-two patients. Of the remaining eight, two had a flat glucose tolerance curve and six were normal. The fasting blood sugar level was measured in all subjects and found to vary from 135 to 200 mg. per cent in fifteen. Of these, ten had varying degrees of glycosuria and clinical symptoms such as polyuria and polydypsia which required suitable dietary regimens and insulin in amounts varying from 10 to 60 units daily. No ketosis was demonstrated in any case, although significant glycosuria was often present. Glucose tolerance tests were performed in all fifty patients and a diabetic curve was obtained not only in the fifteen subjects with hyperglycemia but also in twenty-seven of the thirty-five patients who had no elevation of the fasting blood sugar level.

Hyperglycemia and glycosuria requiring insulin therapy was the first manifestation of Cushing's syndrome in two patients. The diabetes was present for several months before other clinical manifestations of adrenal cortical hyperfunction became evident. In both instances successful treatment of the Cushing's syndrome resulted in cure of the diabetes. In a third patient mild diabetes had been present for twelve years

and had never previously required insulin for adequate control. With the advent of Cushing's syndrome, in this instance due to an adrenal carcinoma, the diabetes became more marked and 40 units of insulin daily was required for control. After removal of the adrenal tumor it was again possible to discontinue the use of insulin.

Eleven patients who had some evidence of disturbance in carbohydrate metabolism prior to treatment of the Cushing's syndrome were again studied after cure of the disease. In all instances both the fasting blood sugar levels and the glucose tolerance curves returned to within normal limits. Four additional patients, with adrenal cortical carcinoma, showed an improvement in carbohydrate metabolism following removal of the tumor but recrudescence of diabetes occurred with the development of functioning metastases.

Urinary Excretion of the Neutral 17-Ketosteroids, Formaldehydogenic Steroids and 17-Hydroxycorticoids. The twenty-four-hour urinary excretion of the neutral 17-ketosteroids [8] was measured in forty-six patients and found to be increased in twenty-three. (Table xv.) The highest values were obtained in the patients with adrenal carcinoma. Six of the nine members of this group had increases in the urinary excretion of these fractions, in contrast to two of six patients with adrenal adenoma and fifteen of thirty-one with non-tumorous adrenal cortical hyperfunction. Thus a marked increase in the daily urinary excretion of the neutral 17-ketosteroids is good, but not incontrovertible evidence of an adrenal cortical carcinoma, while a normal value, or modest elevation, does not exclude this diagnosis. A decrease in the urinary excretion of the neutral 17-ketosteroids has been reported to occur in the presence of adrenal adenoma [9], and was observed in two of our six patients, but was also found in one patient with carcinoma and in four subjects with non-tumorous adrenal hyperfunction. In general, the values obtained in the latter group tended to be higher than those seen in association with adrenal adenoma. No significant difference was apparent in the values observed in patients with Cushing's syndrome who had bilateral adrenal cortical hyperplasia and in those with normal sized adrenal glands. $\Delta_{3,5}$ androstadienone-17 was demonstrated in the urine of two patients, one with adrenal carcinoma, the other with nontumorous adrenal hyperfunction.

TABLE XVI PLASMA LEVELS OF 17-HYDROXYCORTICOIDS

Patients with	No.	Elevated*
Adrenocortical carcinoma	5	5
Adrenocortical adenoma Non-tumorous adrenocortical	3	2
hyperfunction	9	7

^{*} More than 25 γ per cent.

The twenty-four-hour urinary excretion of the formaldehydogenic steroids [10] was measured in twenty-two patients and found to be elevated in all. (Table xv.) In this regard, too, there was considerable overlapping among the various groups, but in general the values obtained in the patients with carcinoma were higher than those in the other groups. The urinary excretion of the 17-hydroxycorticoids [11] was measured in eight patients and was increased in all. (Table xv.)

Plasma Level of the 17-Hydroxycorticoids, Response to Gel-ACTH and to Prednisone Suppression. The plasma levels of the 17-hydroxycorticoids were determined in seventeen patients. These included nine subjects with non-tumorous adrenocortical hyperfunction, three with a benign adrenal tumor, and five with adrenal carcinoma. (Table xvi.) Increased levels were found in fourteen. The values were considerably higher in the patients with carcinoma, although a lesser value does not exclude this diagnosis. Levels within normal limits were obtained in two patients with non-tumorous adrenal hyperfunction and in one patient with a benign adrenal cortical tumor. In all three the urinary excretion of the 17-hydroxycorticoids was increased. Following successful treatment in five patients with non-tumorous adrenal hyperfunction, the plasma level and the urinary excretion of the 17-hydroxycorticoids returned to normal.

The response of the plasma 17-hydroxycorticoids to intramuscular administration of gel-ACTH was studied in seventeen cases by the procedure previously described [12]. In normal subjects an increase in the plasma level of the 17-hydroxycorticoids of from 14 to 30 γ per cent occurs two hours after administration of 40 units of gel-ACTH. Patients with non-tumorous adrenal cortical hyperfunction may show an increased response, while patients with either

Table xvII

RESPONSE OF PLASMA 17-HYDROXYCORTICOSTEROIDS

TO GEL-ACTH

			Response	:
Patients with	No.	Inade- quate	Normal	In- creased
Non-tumorous adrenocortical hyperfunction	9 3 5	1 2	5	3
Adrenocortical carcinoma	5	3	1	1

Note: Inadequate response = increase in plasma 17-OH-CS of less than 14 γ per cent. Normal response = increase in plasma 17-OH-CS of 14 to 30 γ per cent. Increased response = increase in plasma 17-OH-CS of more than 30 γ per cent.

benign or malignant adrenal tumors generally show an inadequate response. In Table xvII are listed the results obtained with this procedure in nine patients with non-tumorous adrenal hyperfunction, three with adenomas and five with carcinomas. Of the first group, an increased response was obtained in three subjects, an inadequate response in one and a normal response in five. Of the three patients with adrenal adenoma, an inadequate response was elicited in two and a normal response in one. An inadequate response was obtained in three of the five subjects with adrenal carcinoma; one showed hyper-responsiveness, and in one the response was within the normal range. Following removal of the adrenal carcinoma the patient who demonstrated an increased response now showed an inadequate response, suggesting that the initial result obtained was due to the responsiveness of the tumor exogenously administered corticotropin [12].

The results of these studies demonstrate that this procedure cannot be relied upon to establish the correct pathologic diagnosis. In general, failure of the plasma 17-hydroxycorticoids to rise appreciably following administration of corticotropin occurs with much greater frequency in patients with tumor, whereas increased responsiveness is observed more often in patients with non-tumorous adrenal hyperfunction. Nevertheless, a normal result excludes neither the diagnosis of Cushing's syndrome nor the presence of an adrenal tumor, benign or malignant. The presence of a marked elevation in the control level of the plasma 17-hydroxycorticoids, which increases slightly or not at all with exogenous corticotropin, is strongly suggestive of adrenal carcinoma.

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Recent studies have demonstrated that the daily administration of 30 to 50 mg. of prednisone to normal subjects for a seven-day period results in suppression of adrenocortical response to exogenously administered corticotropin, as determined by the absence of elevation in the plasma level of the 17-hydroxycorticoids [13]. However, in patients with non-tumorous Cushing's syndrome adrenal responsiveness to corticotropin is not suppressed following this procedure [13,14]. This test was employed in twelve patients, of whom eleven had no adrenal cortical tumor and one had a benign adenoma; this latter patient had originally shown an increase in the plasma steroids following administration of gel-ACTH. Four of the twelve subjects were untreated, five were in complete clinical remission following treatment and three showed a partial remission. In the four untreated patients with non-tumorous adrenal hyperfunction, prednisone failed to induce adrenal suppression, while of the five with complete remission three showed adrenal suppression. Two of these had been completely well for five and eight years following pituitary radiation, and in one an adrenal adenoma had been removed four months previously. Prior to operation injection of corticotropin elicited an increase in the plasma 17-hydroxycorticoids which could not be suppressed with prednisone. The remaining two patients had been well for approximately one year following unilateral adrenalectomy and pituitary radiation. In both, results of the suppression test continued to be abnormal and in one evidence of recurrence of the Cushing's syndrome subsequently developed. Of the three patients in partial remission one showed normal suppression with prednisone, one did not, and in the third only partial suppression could be induced. The patient who had no response to the suppression test after pituitary radiation and unilateral adrenalectomy eventually required total adrenalectomy for relief of the Cushing's syndrome; the subject with a partial response showed gradual but continuous improvement; while the third patient, with a normal response to prednisone suppression, showed a complete remission several months later.

The results of these studies indicate that the suppression test is of value in the diagnosis of Cushing's syndrome. Such a response generally indicates the presence of non-tumorous adrenal hyperfunction but does not exclude tumor when a prior ACTH test has shown an increase in

the plasma 17-hydroxycorticoids. Persistence of an abnormal suppression test after treatment should raise the suspicion of persistence of the underlying disease process.

X-Ray Visualization of the Adrenals. The crucial problem in considerations of the treatment of Cushing's syndrome is the differentiation of tumor from non-tumorous adrenal cortical hyperfunction. The value of proper roentgen studies in the detection of adrenal tumor, particularly with the use of perirenal or presacral gas insufflation, is well established [15-18]. The adrenal x-ray studies in this report deal with observations on fifty-seven patients. (The additional seven patients are not included in the general body of this paper, since they are of recent origin and adequate follow-up studies are not yet available.) The roentgen examination, in sequential order, included a scout film of the abdomen, intravenous pyelography and presacral or perirenal gas insufflation, often with concomitant intravenous pyelography and tomography. In fifty-two of the fifty-seven patients the nature of the adrenal lesion was proved by exploration or at postmortem examination; in the remaining five the subsequent clinical course following treatment attested to the absence of tumor.

There were fourteen cases of adrenocortical carcinoma (Table xvIII), equally distributed between the right and left sides, and varying in weight from 30 to 910 gm. In seven a scout film of the abdomen revealed a soft tissue mass lying above the upper pole of the kidney. Calcification was demonstrable in two of these tumors, and in four the kidney was pushed downward. Intravenous pyelography was performed in thirteen members of this group, and in seven the kidney was found to be displaced downward and, occasionally, either medially or laterally. In some instances the upper calyces were irregular and incompletely filled. Tomography without gas insufflation was successfully utilized in two patients to demonstrate the presence of a suprarenal mass. It was thus possible, by means of scout film, intravenous pyelography and tomography, to demonstrate an adrenal tumor in nine of the fourteen cases of carcinoma. The tumors undetected by these means weighed 55, 100, 144, 170 and 400 gm., respectively. The smallest tumor demonstrated with these technics weighed 30 gm. and was 4 cm. in diameter; it was in an eleven month old infant.

Gas insufflation x-ray studies were performed

TABLE XVIII
CARCINOMA OF THE ADRENAL (FOURTEEN CASES)

Sex	Age (yr.)	Side	Size (cm.)	Weight (gm.)
F	1	R	4.5 × 4 × 3	30
F	33	L	$5.5 \times 5 \times 2.8$	55
M	59	R	$8 \times 4.5 \times 4$	144
F	34	L	$8.5 \times 6 \times 3.5$	130
F	35	R	$9 \times 7 \times 4$	170
F	63	L	$10 \times 6 \times 4$	100
F	69	L	$10 \times 6 \times 5$	148
F	35	R	10	
F	35	L	(greatest diameter) 10 (greatest diameter)	***
F	36	R	11	400
F	49	R	(greatest diameter) 13 × 10 × 7	375
F	37	R	$14 \times 10 \times 5$	
F	19	L	$17 \times 13 \times 11$	860
F	60	L	$17 \times 14 \times 8$	910

in ten of the fourteen patients. (Table xix.) In eight an adrenal mass was demonstrated and proved to be present at either operation or postmortem examination. Thus, in three of the five patients in whom an adrenal tumor was not evident with the simpler and more conventional x-ray technics, gas insufflation studies established the presence of such a tumor. Employing all available roentgenologic technics, a correct diagnosis was established in twelve of fourteen patients with adrenal carcinoma. (Table xx.)

There were nine instances of adrenal cortical adenoma. The weights in seven varied from 6 to 24 gm. (Table xxi.) In no instance was the diagnosis of tumor possible on the basis of a scout film of the abdomen or following the use of intravenous pyelography. Gas insufflation studies were performed in the nine patients, and in six a correct diagnosis of adrenal tumor was established. In one, the tumor weighed only 6

Table XX
COMBINED RESULTS OF PLAIN FILMS, INTRAVENOUS
PYELOGRAM AND GAS INSUFFLATION STUDIES IN
TWENTY-THREE PATIENTS WITH ADRENAL
TUMORS

Patients with	No.	Correct Diagnosis
Carcinoma	14	12
Adenoma	9	6

Table XIX
PERIRENAL AND RETRORECTAL GAS INSUFFLATION
STUDIES

Patients with	No.	Correct X-Ray Diagnosis	Incorrect X-Ray Diagnosis	Technically Inadequate		
No tumor	31	23	4	4		
Adenoma		6	3	0		
Carcinoma	10	8	1	1		
Total	50	37 (74%)	8 (16%)	5 (10%)		

gm. and measured 2.5 cm. in its greatest diameter. In the remaining three patients a right-sided adrenal cortical tumor was found at operation. These tumors weighed 9.6, 10 and 15 gm.

Thirty-four patients had non-tumorous adrenal cortical hyperfunction. In all, a plain film of the abdomen and intravenous pyelography failed to reveal evidence of tumor. Gas insufflation studies were utilized in thirty-one instances and tomography was concurrently employed in twenty-four. In four patients the procedure was technically unsatisfactory. In twenty-three the adrenal glands were demonstrated to be either normal in size or slightly and bilaterally enlarged, with no evidence of tumor. These findings were confirmed at operation in twenty, and in three by the long-standing remission induced by pituitary radiation. In the remaining four patients, in two of whom tomography was employed, an incorrect diagnosis of adrenal tumor was made, probably because of inability to distinguish between tumor and adrenal fat pads.

The results of these studies suggest that the diagnosis of adrenal carcinoma can usually be made roentgenologically if the various technics

TABLE XXI
ADRENAL ADENOMA (NINE PATIENTS)

Sex	Age (yr.)	Side	Size (cm.)	Weight (gm.)
F	46	R	2.2	10
F	37	L	2.5	6
F	47	L	2.5	8.5
F	28	R	3	9.6
F	41	L	3	24
F	25	R		15
F	34	R	4	
F	30	L	4	
F	37	R	4	17

TABLE XXII
ADRENAL PATHOLOGY

Mount Sinai Hospital Scries (45 cases)		Cases Collected from Literature [15] (97 cases)	
No.	%	No.	%
13	32.5	16	16.5
8	20	11	11.3
11	27.5	58	60
13	32.5	9*	9.2
	No.	No. % 13 32.5 8 20 11 27.5	Hospital Series (45 cases) from Lite (97 cases) No. No. No. No.

^{*} Plus two cases of infarcted adrenals and one of hypoplastic adrenals.

currently available are employed. Recognition of adrenal cortical adenomas by these means is less successful, since they are usually appreciably smaller than the carcinomas. Hence, demonstration of a suprarenal mass in Cushing's syndrome with a scout film of the abdomen or by the use of intravenous pyelography points to the probable presence of a carcinoma. The roentgen demonstration of calcification in the adrenal mass does not argue against the diagnosis of carcinoma. Failure to demonstrate an adrenal tumor even by all available x-ray technics does not exclude the possible presence of such a tumor.

THE PATHOLOGY OF CUSHING'S SYNDROME

Postmortem examination was performed in thirteen patients, eleven females and two males. Seven of this group had adrenal cortical carcinoma, four adrenal adenoma, and two had non-tumorous adrenal cortical hyperfunction. Studies of the pathology of the adrenals were made in thirty-two additional patients in whom one or both adrenal glands were surgically removed.

Adrenal Glands. An adrenal tumor was present in twenty-one patients, in thirteen of whom the tumor was malignant. In twelve patients the contralateral adrenal also was examined. In nine this adrenal was found to be small, approximately 3 gm. in weight, and atrophic on histologic examination. However, in three patients, two with carcinoma and one with adenoma, the contralateral adrenal was normal in size, the weight varying from 6.7 to 7.5 gm. In twenty-four patients no adrenal tumor was

found. The adrenals were enlarged in eleven, varying in weight from 8.5 to 17.5 gm. Three had several nodules in the cortex, which ranged in size from 1 to 3 mm. in diameter. In thirteen patients the adrenals were normal in size and did not exceed 8 gm. in weight. Histologic studies of the latter glands, employing routine staining methods, did not reveal any significant changes, but special histochemical staining technics were not employed in these instances No definite correlation was evident between changes in width or structure of the zona reticularis and the degree of virilism manifested clinically. In Table XXII these data are compared with those collected from the literature and reported by Plotz, Knowlton and Ragan [15].

The seven patients with adrenal carcinoma in whom postmortem examination was performed had metastases: five in the regional lymph nodes, five in the lungs, four in the liver, three in the spine, and one in a lymph node in the left supraclavicular fossa. In two patients the tumor had extended through the suprarenal veins into the inferior yena caya.

Adenohypophysis. The pituitary gland was examined in nine patients, five with adrenal cortical carcinoma, two with an adrenal adenoma and two with non-tumorous adrenal cortical hyperfunction. The staining technics employed included the hematoxylin and eosin stain, Mallory's acid fuchsin-aniline blue method, and Crooke's modification of the Mallory method. The findings in the adenohypophysis were essentially normal in three patients with adrenal carcinoma and in two with adrenal adenoma. In two others with adrenal carcinoma and in the two with non-tumorous adrenal cortical hyperfunction, multiple vacuoles and areas of hyalinization in the cytoplasm of the basophils were found. In one patient with adrenal carcinoma some eosinophils exhibited similar vacuoles in the cytoplasm, although no hyalinization was present. In two others, one with an adrenal carcinoma and one without adrenal tumor, the number of basophils appeared moderately reduced, while the eosinophils were increased. In another patient with non-tumorous adrenal hyperfunction the number of eosinophils was strikingly decreased. None of the nine subjects showed basophilic adenomas. In the studies reported by Plotz, Knowlton and Ragan [15] a basophilic adenoma was present in twenty-four of fifty-eight patients with adrenal hyperplasia and in three of nine with normal adrenals. In

addition, three patients had a mixed basophilic and chromophobe adenoma and six had chromophobe adenomas. Eight subjects showed an increased number of basophilis and basophilic invasion of the posterior lobe.

Thyroid and Parathyroids. The thyroid gland was examined in thirteen patients, seven with adrenal carcinoma, four with adrenal adenoma and two with non-tumorous adrenal cortical hyperfunction. In nine, the thyroid was of normal size, weighing less than 20 gm. These patients included five with adrenal carcinoma, two with adrenal adenoma and two without tumor. One patient with an adrenal carcinoma had a diffusely enlarged thyroid. Another had a multinodular goiter. Two patients with adrenal adenoma had solitary colloid adenomas. In the patients with non-tumorous adrenal hyperfunction the thyroid alveoli appeared large, packed with colloid, and lined by a single layer of low cuboidal epithelium. The parathyroids were examined in seven patients. Four showed some fatty infiltration but were otherwise normal.

Thymus. Information on the thymus was available in six patients. In one, the thymus was reported as normal. In five, the only evidence of thymic tissue was the presence of an occasional thymic corpuscle scattered through the fat tissue. The ages of these patients were twenty-three, thirty-four, thirty-six, thirty-seven and forty-seven years. Under normal circumstances one would not expect to find such almost complete disappearance of thymic tissue [19]. This finding presumably is explained by the thymolytic effect exerted by the excessive elaboration of adrenal steroids.

Pancreas. The pancreas was examined in thirteen patients. Old areas of fat necrosis were present in four, a considerable increase in fat in the interstitial tissue in three and diminution in the number of the islets of Langerhans in two.

Testes. The testes were studied in two patients, one a twenty-three year old subject with non-tumorous adrenal cortical hyperfunction, the other a fifty-nine year old subject with adrenal cortical carcinoma. In both the testes were slightly decreased in size and somewhat soft in consistency. In the first patient the tubules were found to be small and showed maturation arrest at the primary spermatocyte stage; Leydig cells were absent and there was no significant amount of fibrosis. The testes of the second patient showed marked atrophy of the tubules with moderate fibrosis of their walls. The semi-

niferous epithelium was scant and consisted only of spermatogonia and Sertoli cells. In this instance, too, the Leydig cells were entirely absent.

Ovaries. The ovaries were studied in ten subjects, five with adrenal carcinoma, four with adenoma and one with bilateral adrenal cortical hyperplasia. Six patients varied in age from thirty to thirty-seven years, two were forty-seven and forty-nine, and two were sixty-three and sixty-nine years old. In the latter four patients the ovaries were indistinguishable from those seen in normal women of comparable age. The ovaries of the other six patients were normal or somewhat small in size, whitish in color, and showed a sharp reduction in all phases of follicular activity. In addition, the number of primordial follicles appeared to be reduced. Small cortical cysts and stromal fibrosis were infrequent. Patchy thickening and fibrosis of the tunica albuginea were often present. There was no evidence of perifollicular theca cell hyperplasia or luteinization. The changes in the younger age group suggested a process of premature aging. The findings in the ten patients were not those seen in "Stein-Leventhal" ovaries.

Brain. The brain was examined in eight patients. Internal hydrocephalus was found in five, and cortical atrophy in three women aged thirty-six, thirty-seven and forty-seven years. The weight of the brain in the latter three patients was 1,040, 1,060 and 1,030 gm. Microscopic examination showed an increase in the perivascular spaces. These findings are similar to those previously reported by Trethowan and Cobb [20], and Cope and Raker [21]. Examination specifically of the hypothalamus in three patients, two with adrenal carcinoma and one with bilateral adrenal hyperplasia, revealed no abnormalities. In one patient with an adrenal adenoma the pineal gland was found to be normal.

Cardiovascular System and Kidneys. The heart was normal in size and weight in four patients, slightly hypertrophied in three and considerably enlarged in six in whom the weight of the heart varied from 475 to 560 gm. and the thickness of the wall of the left ventricle was greater than 20 mm. The average duration of Cushing's syndrome before death was 1.5 years in the patients with normal-sized hearts, 1.7 years in those with slight cardiac hypertrophy, and 4.8 years in those with more pronounced cardiac

hypertrophy. (Twelve patients had had elevation of both systolic and diastolic blood pressure levels; the one normotensive subject had a normal-sized heart.)

Atherosclerosis of the aorta, coronary and cerebral vessels was marked in two patients, one aged twenty-three and the other forty-seven years. Both had had hypertension. A few small atheromatous plaques were present in the vessels of eight patients; no significant atherosclerotic changes were found in the remaining three. The average duration of Cushing's syndrome was five years in two patients with marked atherosclerosis, 2.5 years in eight patients with slight atherosclerotic change, and 1.3 years in three patients who showed no such changes.

Arteriolosclerosis involving the kidneys, pancreas, spleen, liver and adrenals was found in five patients, whose ages varied from twenty-three, to forty-nine years. All showed varying degrees of nephrosclerosis, and in two necrotizing lesions of the renal arterioles were present. The blood pressure had been markedly increased and cardiac hypertrophy was pronounced in all five. In the remaining eight subjects no sigficant arteriolosclerosis could be demonstrated.

Skeleton. Moderate to marked osteoporosis of the vertebral bodies and the ribs was present in nine of the thirteen patients, four of whom were less than thirty-eight years of age. Pathologic fractures were present in five instances, four involving the ribs and two the dorsal vertebrae. In three patients with rib fractures, rings of firm bone-like tissue were found on both sides of the fracture lateral to the costochondral junction. Microscopic examination of these areas revealed that infraction of the cortex had occurred and new bone had formed. The medulla of the ribs in this region contained overgrowth of bone and connective tissue.

Liver. In six patients examination of the liver revealed no abnormalities, while in four a moderate fatty infiltration was observed. In three subjects, one with an adrenal adenoma and two with adrenal carcinoma, severe and extensive fatty infiltration was present. Similar changes were described by Steinberg, Webb and Rafsky [22] in a patient treated with cortisone.

Gastrointestinal Tract. Three chronic prepyloric ulcers were found in one patient with adrenal carcinoma who had had signs of Cushing's syndrome for almost five years. An acute prepyloric ulcer was present in another woman with an adrenal carcinoma and manifestations of Cushing's syndrome of one year's duration. No evidence of peptic ulceration, past or pressent, was demonstrable in the remaining eleven patients. Five had solitary or multiple polypi of the large bowel.

Skin and Muscles. Microscopic examination of the violaceous striae was made in three instances. There was considerable atrophy of the epidermis and corium, with moderate hyperkeratosis. The capillaries and venules were dilated and thin-walled. In two, the dilatation of the vessels was so pronounced as to suggest telangiectasia. The space between the endothelial cells in such vessels was widened and hemorrhage due to diapedesis was present in many areas. The endothelial cells appeared normal.

The striated muscles of the extremities, abdomen and thorax were grossly pale, soft, atrophic and friable. Histologic examination revealed atrophy of muscle fibers, many with extensive infiltration with fat.

THE TREATMENT OF CUSHING'S SYNDROME (TABLE XXII)

The presence of an adrenal cortical tumor calls for prompt surgical removal. Prior to the advent of the glucogenic steroids such surgery was associated with considerable early postoperative mortality due to the fact that the contralateral adrenal was often atrophic. Of our eight patients with adrenal adenoma, four died within twelve to seventy-two hours after operation. These deaths occurred prior to the advent of cortisone, cortisol and corticotropin, and death ensued despite preparation and subsequent treatment with whole adrenal cortical extract and desoxycorticosterone acetate. An additional patient died of severe nephrosclerosis and intracranial bleeding two and a half months after operation. Three patients have been in complete remission for two and a half, six and ten years. These were prepared for surgery as follows: On the morning of the operation 50 mg. of cortisone acetate was administered intramuscularly, and again immediately preoperatively. During the operative procedure 100 mg. of cortisol hemisuccinate (Solu-Cortef®) was administered intravenously. The patients continued to receive 50 mg. of cortisone acetate intramuscularly every six hours postoperatively until the hormone could be administered orally. Occasionally it was found necessary dur-

Table XXIII
TREATMENT OF CUSHING'S SYNDROME (FORTY-FOUR PATIENTS)

	No Adrenal Tumor		Adrenal Carcinoma		Adrenal Adenoma	
Therapy	No. of Patients	No. with Remission	No. of Patients	No. with Remission	No. of Patients	No. with Remission
Pituitary radiation*	14	7				
Unilateral adrenalectomy†	7	4	13	2	8	3
Pituitary radiation and unilateral adrenalectomy	2	1				
Total	23	12	13	2	8	3
Duration of remission (yr.)	2 to 14		2½ to 10		2 to 11	

* Of the seven patients who failed to respond to pituitary radiation alone, five subsequently had a unilateral adrenalectomy; four of these had a complete remission.

† Of the three patients who failed to respond to unilateral adrenalectomy alone, one subsequently received pituitary radiation followed by a complete remission. Of the twenty-three patients without adrenal tumor, seventeen had complete remissions following one or more of these procedures.

ing the immediate postoperative period to repeat the intravenous administration of cortisol. Following surgery the daily amount of hormone was gradually reduced and finally discontinued. This may take from two weeks to several months. Development of arthralgias, erythematous eruptions, nausea and vomiting, abdominal pain, hypotension and asthenia are indications for continued or increased administration of steroid. Intermittent use of corticotropin in an effort to stimulate the function of the contralateral adrenal is favored by some.

Patients with carcinoma of the adrenal cortex were managed similarly. Of thirteen such patients, one is in a complete remission for eleven years and another for two years. The remaining eleven patients died within five months to two and a half years after the operation.

The chief problems of treatment center essentially around those patients in whom no adrenal tumor is present. Twenty-three patients with non-tumorous adrenal cortical hyperfunction were treated with pituitary radiation, unilateral adrenalectomy, or a combination of both measures. In seventeen satisfactory remissions developed. Fourteen were treated with pituitary radiation alone. They received 3,800 to 4,000 r delivered to the pituitary over a thirty-nine to fifty-two-day period. Seven have had a complete remission, which has thus far lasted six and a half, eight, nine, nine and a half,

ten and a half, twelve and fourteen years, respectively. Of the seven patients who failed to respond, five subsequently had a unilateral adrenalectomy. In three of this group satisfactory remissions developed which have continued for two and a half, four and twelve years. In one patient a remission developed which lasted for two years, followed by recurrence; another had no improvement. Both required removal of the remaining adrenal.

Seven patients had a unilateral adrenalectomy as the only or first form of therapy. Four have had a complete remission for four, six, seven and nine years. One patient had a remission for one year, followed by a recurrence which necessitated removal of the other gland; an additional patient showed no response to unilateral adrenalectomy but responded with complete remission to a subsequent course of pituitary radiation. This remission has thus far continued for seven years. The third patient who failed to respond to unilateral adrenalectomy was lost to our follow-up after an eight-month period.

Two subjects were treated by unilateral adrenal ectomy, followed within one or two weeks after operation by pituitary radiation. One has a complete remission thus far of two years' duration, the other failed to show any response and required removal of the remaining adrenal.

Probably no more than one-third of all

patients with non-tumorous adrenal cortical hyperfunction require bilateral adrenalectomy. The others will respond well either to pituitary radiation alone or to a combination of unilateral adrenalectomy followed almost immediately by pituitary radiation. The clinical response is directly related to the amount of radiation; an adequate response is infrequently obtained when the roentgen dosage delivered to the pituitary body is less than 4,000 r. Ample time, often in excess of six months, must be allowed for the development of a satisfactory remission. Such a prolonged period is not feasible in patients with severe hypertension and renal or cardiac failure, and perhaps in patients with severe osteoporosis and pathological fractures. Under these circumstances immediate bilateral adrenalectomy is desirable.

We have observed no ill effects following pituitary radiation. Three young women who were amenorrheic before treatment became pregnant and gave birth to normal children after treatment. One had two courses of pituitary radiation eight months apart, one had one course and a unilateral adrenalectomy, and the third had two courses followed by bilateral adrenalectomy. In none of seventeen patients who received one or two courses of pituitary radiation did intracranial, ocular or thyroidal abnormalities develop. Those who were cured had no evidence of impairment of adrenal function. Local alopecia at the site of radiation generally develops, but regrowth of hair has uniformly occurred within several months after completion of

Prognosis. Adequate follow-up studies are available in our fifty cases. Twenty-five are alive and well, twenty-five have died. Eleven of the thirteen patients with adrenal carcinoma, five of the eight with benign adrenal cortical tumor, and nine of the twenty-nine with nontumorous adrenal cortical hyperfunction have died. Four of the five patients with adrenal adenoma who died were operated upon prior to availability of the glucogenic steroids. Such mortalities are avoidable today. Nine patients died of carcinomatous metastases. The remaining subjects died primarily of the complications of severe hypertension. These included intracranial vascular accidents, cardiac failure, nephrosclerosis with uremia, and coronary thrombosis. Two patients died as a result of uncontrollable sepsis.

It is possible with appropriate treatment to

effect disappearance of the manifestations of the disease. The menses returned in the previously amenorrheic women who were within the childbearing age, and five of these patients subsequently became pregnant and were delivered of normal babies. The mental disturbances subsided with a return to the pre-illness personality pattern. Of nineteen patients who had hypertension before treatment and in whom sufficient information is available, the blood pressure returned to normal levels in fourteen. while in five hypertension persisted. White blood cell counts and differential studies were repeated in thirteen patients after successful treatment, and in all there was a reduction in the number of polymorphonuclear leukocytes and an increase in eosinophils and lymphocytes. Six patients who had an increase in serum sodium levels prior to therapy had a return to normal values and in three a previously elevated blood CO2 content was reduced. In five patients with increased serum alkaline phosphatase, values after treatment were available and all showed a return to normal levels. In every patient treated successfully the previously increased urinary excretion of the neutral 17-ketosteroids and 17-hydroxycorticoids and elevated plasma 17hydroxycorticoid level returned to normal. Fasting blood sugar determinations and glucose tolerance tests were performed in sixteen patients after conclusion of therapy. Two had had diabetes requiring insulin therapy as the first manifestation of the Cushing's syndrome; in both the use of insulin could be discontinued after treatment; the glycosuria disappeared, and the fasting blood sugar levels and glucose tolerance curves were now normal. In five patients with adrenal carcinoma there was a temporary decrease in the glycosuria and fasting blood sugar levels after removal of the tumor. In nine patients with non-carcinomatous adrenal cortical hyperfunction the fasting blood sugar levels returned to normal values and the glucose tolerance curves became either normal or flat.

In ten patients, x-ray studies of the spine and ribs were repeated two to twelve and a half years after onset of the remission. All had manifested extensive bony demineralization before treatment and six had compression fractures of several vertebrae and multiple rib fractures. With remission there was no appreciable decrease in the osteoporosis, although no new fractures of the vertebrae or ribs occurred and bone pain subsided. In three patients who were

fifteen years of age or less x-ray studies revealed the presence of new bone, laid down by the epiphyseal end plates of the vertebrae, around the apparently permanently altered bone.

SUMMARY

Clinical and laboratory data are reported in fifty patients with Cushing's syndrome. Thirteen patients had adrenal carcinoma, eight a benign adrenal tumor, and in twenty-nine the Cushing's syndrome was associated with non-tumorous adrenal cortical hyperfunction. One or both adrenals were examined in twenty-four patients with non-tumorous adrenal cortical hyperfunction. In thirteen the adrenals were found to be normal in size, in eleven they were enlarged. The presence of an adrenal cortical tumor could be correctly established by perirenal or retrorectal gas insufflation in three-fourths of the tumor group.

The incidence of the various clinical signs and symptoms is indicated and the relationship of these manifestations to the underlying adrenal pathology is examined. Some electrolyte abnormality was demonstrable in half of the patients; evidence of disturbance in carbohydrate metabolism was obtained in almost all. The urinary excretion of neutral 17-ketosteroids was increased in half the patients with nontumorous adrenal cortical hyperfunction, onethird of the group with a benign adrenal tumor and two-thirds of those with adrenal carcinoma. All patients had an increase in the urinary excretion of either the formaldehydogenic fractions or the 17-hydroxycorticoids. Seven of the nine patients in whom the plasma level of the 17-hydroxycorticoids was determined demonstrated an increase. The response of the plasma level of the 17-hydroxycorticoids to the intramuscular administration of corticotropin, and also prednisone suppression studies, were of value in establishing the presence or absence of an adrenal tumor before operation.

Treatment was determined by the nature of the adrenal pathology. Adrenal tumors were removed surgically, with proper preoperative preparation and postoperative care. In non-tumorous adrenal cortical hyperfunction, pituitary radiation, unilateral adrenalectomy, or a combination of both measures, were employed. In approximately 75 per cent of this group a satisfactory remission was obtained. The remaining patients required bilateral adrenalectomy.

Treatment was followed by complete disappearance of the clinical and laboratory abnormalities in some cases. The roentgen evidence of osteoporosis, however, remained unaltered, although bone pain subsided and spontaneous fractures no longer occurred.

Postmortem studies were made in thirteen patients and the findings are recorded.

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Segmental Consolidation of the Lung*

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THE concept of the bronchopulmonary segments as the basic unit of pulmonary anatomy has long been essential to the thoracic surgeon, chest physician and radiologist. It is now becoming important to many internists. On this account it is thought worthwhile to review our knowledge of the segments and to present an atlas of the segmental consolidations.

First, Ewart [1] in 1889, then Kramer and Glass [2] in 1932 recognized the need to establish a smaller and more accurate unit of localization than the lobe. This was designated by the latter authors as the bronchopulmonary segment and defined as that part of the lung supplied by a primary branch of a lobar bronchus. It represented in their words "not only an anatomic but a pathologic unit."

In 1943 the earlier classifications were superseded by the nomenclature of Jackson and Huber [3]. (Table 1.) This has been accepted as the official system in the United States, and was modified only slightly in the versions accepted by the International Society of Otorhinolaryngologists and the British Thoracic Society [4].

Although the segments occur as described with remarkable constancy in general, there are numerous individual variations in bronchial positions and segmental size. These have been classified and their frequency determined by the detailed studies of Boyden [5]. Classic anatomic studies of the segments were made also by Foster-Carter and Hoyle [6], Brock [7] and others.

PATHOLOGY OF SEGMENTAL CONSOLIDATIONS

Solidification or consolidation of a segment may result from many causes, such as exudates of infection, infiltrations by neoplasms, edema and blood secondary to infarction or aspiration. In addition there may be "drowning of a lung" which refers to the consolidation of a portion of lung by the accumulation of mucus distal to a bronchial obstruction. Ischemic necrosis may result from pulmonary embolism or interference with the blood supply by tumor, infection or surgical accident.

Atelectasis also tends to complicate the process of consolidation, as described in the words of Foster-Carter and Hoyle [6] "true consolidation and true collapse are comparatively rare. It is only possible to say that one or the other predominates . . . In nearly all so-called consolidations, the radiographic shadow is smaller than would be expected owing to associated collapse. And, conversely, there is always some consolidation in a collapsed segment."

Bronchogenic carcinoma provides one of the most complicated pictures. A segmental pneumonia may develop and completely resolve in spite of a partially obstructing neoplasm. A more severe infection may lead to destruction of the lung and abscess formation distal to the tumor. A peripheral neoplasm may become necrotic and simulate abscess. The neoplasm may invade the segment, or ischemic necrosis and hemorrhage may result from invasion of the segmental vessels. Finally, sterile consolidation

Table 1

Jackson-Huber nomenclature of segments of
The Lung

Right Lung	Left Lung				
Upper lobe	Upper lobe, upper division				
1. Apical segment	1, 2. Apicoposterior segment (apical				
2. Posterior segment	segment*) (posterior segment*)				
3. Anterior segment	3. Anterior segment				
Middle lobe	Upper lobe, lower division (lingula)				
4. Lateral segment	4. Superior segment				
5. Medial segment	5. Inferior segment				
Lower lobe	Lower lobe				
6. Superior (apical*) seg- ment	6. Superior (apical*) segment				
7. Medial basal segment	7, 8. Anterior-medial basal (anterior				
8. Anterior basal segment	basal*) segment				
9. Lateral basal segment	9. Lateral basal segment				
10. Posterior basal segment	10. Posterior basal segment				

^{*} Modifications of the international nomenclature.

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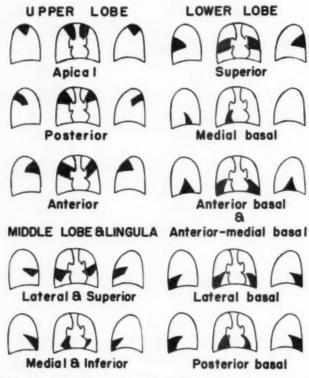


Fig. 1. Roentgenographic projections of segmental consolidations.

may occur by the process of accumulation of mucus behind an obstructing tumor.

Chronic partial obstruction of a lobar or segmental bronchus by tuberculous, fungus or non-specific lymphadenopathy may result in recurrent segmental infections, hemoptysis and chronic productive cough. Because this most often occurs in the middle lobe, it has been referred to as the "middle lobe syndrome" [8], although it is by no means confined to the middle lobe.

Primary pneumonias occur segmentally, as do lesions secondary to the obstructive bronchial diseases. Most pneumonias will be found to lie within the bounds of one or two segments [9]. The older concept of "lobar pneumonia" referred to a classic pathologic process with inexorable evolution into homogeneous consolidation of a large portion of a lung or lobe. Whether this was anatomically segmental or lobar was not considered in the definition. In the light of our present anatomic knowledge it would seem that the term lobar pneumonia should be applied only when the disease is truly lobar. Thus localized pneumonias should be designated segmental or lobar, with either partial or complete consolidation.

ROENTGENOGRAPHIC APPEARANCE OF SEGMENTAL CONSOLIDATIONS

Physicians have become aware that pulmonary disease appears on the roentgenogram as localized patches of opacity, not in a random or haphazard manner, but in the distribution of the segments of the lung. This has lent increased meaning to roentgenographic interpretation.

The segments are separated by fibrous septae which are not visible on the roentgenogram but they border on the visible fissures and the periphery of the lungs so that individual segmental consolidations are usually readily identified. Although segments vary in size and subsegmental portions normally belonging to one may be annexed by an adjacent segment, they are constant enough to cast specific shadows on the frontal and lateral films. The patterns of the consolidation of the separate segments have been determined by metal, plastic and gelatin injections of lungs [6], by studies of bronchograms [10], and by combined anatomic-roentgenographic studies of intact lungs in cadavers [11].

Whereas most diagrams of the segmental anatomy of the lungs depict the surface distribution of the segments, it is the two-dimensional projection of the segments on the frontal and lateral chest roentgenograms which is of major importance. Descriptions of the roentgenographic appearance of consolidated segments have appeared in several articles [6,10,12]. In our experience individual consolidations of the segments have appeared as shown in Figure 1.

While roentgenographic localization is usually possible it should be pointed out that anomalies and distortion of normal segmental positions by atelectasis or chronic lung disease may make correct anatomic diagnosis difficult. The anomalies and variations of segmental anatomy have been studied by Boyden [5] and others [13,14]. Some of these should be discussed.

ANOMALIES OF BRONCHOPULMONARY ANATOMY

The major fissure dividing the upper and middle lobes from the lower lobe on the right, and the upper from the lower lobe on the left, is complete in only 70 per cent of persons. The minor fissure on the right between the upper and middle lobe also is often incomplete, and is visible on frontal films only 50 per cent of the time.

The azygous lobe is not a lobe but merely

the part of the apex of the lung demarcated by a partial fissure. This is formed by the azygous vein indenting the posterior surface of what is chiefly the apical segment of the right upper lobe. It is present to some degree in 1 per cent of the population and visible on the postero-anterior roentgenogram in 0.5 per cent, outlining roughly, although not exactly, the apical segment on the right.

The lateral subsegment of the posterior or anterior segment of the upper lobes exists as a separate segment in approximately 10 per cent of the population. This portion of the lung is of great significance because of its vulnerability to

aspiration and lung abscess.

In 8 per cent of patients, the lingula is separate from the upper division of the left upper lobe

forming a "left middle lobe."

In 20 per cent there is partial separation of the superior segment from the lower lobe and in 5 per cent this segment exists as a separate lobe. The anomalous horizontal fissure which separates this segment from the lower lobe is called the superior accessory fissure and the lobe is the superior accessory lobe or Devés lobe.

Flat, plate-like extra segments are present at the base of the superior segments about 60 per cent of the time on the right and 30 per cent on the left. These are supplied by direct subsuperior segmental bronchi from the lower lobe bronchi. Lung abscesses secondary to aspiration tend to occur in these segments.

Similarly, some degree of separation of the medial basal segment on the right occurs 30 per cent of the time and the lateral portion of this pleuralization is seen in 10 per cent of films as the inferior accessory fissure. The medial basal segment may even become an inferior accessory lobe, such as normally exists in cattle.

A rare anomaly is an extra segment usually wedged into but separate from the posterior basal segment of either lower lobe. Such sequestrations of the lung are supplied by an artery directly from the aorta which frequently arises below the diaphragm. Although there is no bronchial or vascular connection with the normal lung, such sequestered segments are subject to infection and cystic degeneration, and may perforate into the normal bronchial structures resulting in abscess cavity or air-filled cysts.

For more detailed information on the variations of bronchopulmonary anatomy, reference should be made to the work of Boyden [5].

SIGNIFICANCE OF SEGMENTAL ANATOMY

The major value of knowledge of the pulmonary segments has been, of course, for the thoracic surgeon and for the internist and radiologist who help in the election of segmental resection. Application of this knowledge has permitted the selective removal of localized disease with maximum preservation of lung tissue and pulmonary function. It was this need which impelled better understanding of segmental anatomy and has given it great impetus in recent decades.

Beyond this specialized need for knowledge, awareness of the segments provides important insight into the pathogenesis of pulmonary disease. Brock's [7] remarkable study of lung abscess established the importance of the subject by localizing predisposed segments and the proper postural positions for optimal drainage of the segments involved. By establishing the role of simple gravitational flow of aspirated material in the genesis of abscess by what he called "bronchial embolism," Brock demonstrated the value of the segmental approach in understanding the pathogenesis of lung abscess as well as in devising rational treatment.

Another important result of such study is the greatly increased value of written descriptions of pulmonary disease when exact segments can be described rather than "zones" or "lung fields." The lamentable loss or destruction of old films would be less distressing if disease had been localized originally to specific segments. For example, a pneumonia identified in old records only as "in the right mid-lung field" could have been in the anterior segment of the upper lobe, the superior segment of the lower lobe, or the lateral segment of the middle lobe. If a second pneumonia should later occur in the same area it would be very important to know if it were in the same segment, for if it were, there would be a strong likelihood of an underlying structural abnormality such as bronchiectasis or partial bronchial obstruction for which surgery may be required. It would seem that some attention to the segments is as much in order as is awareness of the regions of the abdomen or the possible sites of myocardial infarction.

The diagnostic value of knowledge of segments has been pointed out by Kane [12] who stated "the . . . segments constitute important anatomical facets in the analytical and deduc-

tive interpretation of chest x-ray shadows." For example, disease simultaneously involving segments of the upper and lower lobes or of the upper and middle lobes strongly favors the diagnosis of suppuration over neoplasm [14]. Another application of the segmental approach was Kirby's [15] experience that even slowly resolving pneumonitis of multiple segments of the right upper lobe need not be suspected to be due to neoplasm if bronchoscopy with right angle lens revealed no abnormalities.

Further diagnostic applications are afforded by the tendency of certain diseases to affect specific segments. A description of some of these

conditions follows:

Abscess and aspiration pneumonitis, 90 per cent of which are monolobar, chiefly affect the posterior segment of the right upper lobe, superior segments of both lower lobes, lateral aspects of the anterior segments of both upper lobes, the posterior subsegment of the left upper lobe, the superior segment of the lingula and the posterior basal segments of both lower lobes in roughly that order [7]. The segments of the middle lobes are less susceptible to abscess unless by aspiration of dirty water during immersion or by spread of infected secretions from an abscess of an upper lobe or superior segment.

Primary bacterial pneumonias are said to affect chiefly the lower and middle lobes. In our experience the posterior and anterior segments of the upper lobe, the superior segment of the lower lobes and the entire middle lobe and lingula are the parts chiefly affected. Friedländer's pneumonia is said to involve the upper lobes 80 per cent of the time [16]. Staphylococcal pneumonia seems to follow the same pattern.

Bronchiectasis and associated secondary pneumonias tend to occur in the basilar segments, with additional involvement of segments of the lingular, superior and middle lobes in many instances.

Postoperative atelectasis and pneumonitis primarily involve the basilar segments, although either or both segments of the middle lobes may be affected.

The viral pneumonias, primary atypical, psittacosis, Q fever, and the like also have a marked tendency to involve basilar segments, lingular and middle lobe segments in the majority of instances.

Bronchogenic carcinoma produces consolidations which are more often lobar than segmental. As already mentioned a carcinoma partially obstructing a lobar bronchus may be complicated by a secondary pneumonia of only one of the

distal segments. Complete resolution of this pneumonia may produce false reassurance about underlying carcinoma until consolidation of the entire lobe ensues.

Of course, consolidation of any segment may occur as a result of carcinoma of the segmental bronchus, but this phenomenon is most common in the larger segments, i.e., the anterior and posterior segments of the upper lobes and the superior segments of the lower lobes. On the other hand, consolidation of the individual smaller segments of the middle lobe and lingula by carcinoma are uncommon, since tumors tend to consolidate the entire middle lobe and lingula. Peripheral squamous cell carcinoma of the apical segment, with its insidious growth, produces Pancoast's syndrome by local spread to ribs, brachial and cervical sympathetic nerve plexuses.

Infarction also produces segmental lesions, although usually with suggestive pleural changes. These have a strong predilection for the basilar segments.

Primary tuberculosis in childhood resulted in segmental consolidations (epituberculosis) in 24 per cent of 107 cases in an English study [17]. Analysis of ninety cases of segmental atelectasis of primary tuberculosis revealed a predominance of involvement of the entire middle lobe and the anterior, apical and posterior segments of the upper lobes in that order [18].

Isolated lesions occurring in chronic pulmonary tuberculosis have almost exclusive predilection for the apical and posterior segments of the upper lobe. When lower lobe segments are involved they are usually in the superior segment, very rarely in the posterior basal. An analysis of 100 patients with unilateral tuberculosis confined to two segments or less showed that in 70 per cent both apical and posterior segments of the upper lobe were involved, in 20 per cent only the posterior segment, and in 10 per cent only the apical segment were involved [19]. The concept of the Assman infraclavicular focus as the herald of progressive chronic tuberculosis points up the particular importance of the posterior segment of the upper lobes in this disease. On the other hand, isolated tuberculous disease of the anterior segments is extremely rare and carcinoma should be strongly suspected in such lesions. When tuberculosis does occur in an anterior segment only, the odds are one is dealing with primary tuberculosis.

To review these generalizations in another

way: Apical segmental disease is most frequently due to tuberculosis or carcinoma (Pancoast's syndrome). Posterior segmental disease suggests tuberculosis, bacterial pneumonia or aspiration pneumonitis with abscess. Anterior segmental disease should alert one to underlying carcinoma or to aspiration pneumonitis and abscess. Superior segmental disease (of the lower lobes) lacks specificity, characteristically being involved by carcinoma, aspiration pneumonia and abscess, acute bacterial pneumonias and even tuberculosis. Middle lobe and lingular segments when involved individually usually represent instances of bacterial or viral pneumonia or pneumonia secondary to bronchiectasis. When both segments are involved carcinoma, primary bacterial pneumonia or tuberculous lymph node disease usually is the cause. Basilar segments are common sites for infarctions, viral pneumonia, and pneumonitis secondary to bronchiectasis.

EXAMPLES OF SEGMENTAL CONSOLIDATIONS

Figures 2, 3, 4 and 5 are reproductions of frontal and lateral roentgenograms of individual patients showing the characteristic pattern of the consolidation of each of the segments and lobes.

Right upper lobe (Fig. 2). This homogeneous consolidation was produced by the entrapment of sterile mucus distal to a totally obstructing bronchogenic carcinoma.

Upper division of the left upper lobe (Fig. 2). This subdivision is included because it corresponds to the right upper lobe and because it is so often specifically involved by disease. In this instance, as it is frequently, the disease is bronchogenic carcinoma.

The apical segments (Fig. 2) (subsegment on the left) are shown in examples of apical tuberculosis. These segments normally do not overlap the other segments significantly, so the frontal chest roentgenogram is all that is needed. On occasion, an unusually large posterior segment may encroach on this area.

The posterior segments (Fig. 2) (subsegment on the left) involved with primary bacterial pneumonia cast quadrilateral shadows which are very similar to the anterior segments on the frontal projection, even extending out along the minor fissure on the right. By contrast, they show the full extent of the uninvolved apical segments. The lateral views clearly distinguish them from the anterior segments.

The anterior segments (Fig. 2) are shown con-

solidated by bronchogenic carcinoma. The segment on the left has undergone considerable collapse. The anterior segments tend to dip lower beneath the hila than the posterior segments and also extend farther medially above the hila.

The middle lobe and lingula (Fig. 3) are shown as analogous structures typically sparing the costophrenic angles where they do not overlap the lower lobes. Although the bacterial pneumonia of the middle lobe involves other parts of the lung, the middle lobe is well demonstrated. The lingula is completely consolidated by carcinoma and secondary abscess formation.

The lateral segment of the middle lobe and the superior segment of the lingula (Fig. 3) are consolidated by primary bacterial pneumonias. Although collapse of the entire middle lobe or lingula may simulate these patterns, examination of the fissures makes identification fairly certain.

The medial segment of the middle lobe and the inferior segment of the lingula (Fig. 3) characteristically blur the cardiac margins because the consolidated areas are contiguous to the heart rather than overlap it as do the posterior basal segments. This is the so-called "silhouette sign" [13]. The distinction of medial segment consolidation from a collapsed middle lobe is possible by demonstration of the minor fissure on frontal and lateral views. (This has been drawn in on the lateral for better visualization.) The middle lobe disease is a tuberculous pneumonia (secondary to the cavity seen in the posterior segment of the upper lobe). The lingular disease is a secondary bacterial pneumonia due to a carcinoma partially obstructing the left upper lobe bronchus.

The lower lobe (Fig. 3) is outlined by a patchy pneumococcal pneumonia on the right which would not qualify as a classic "lobar pneumonia" of the past, for penicillin produced rapid resolution before consolidation was complete. On the left there is consolidation and abscess due to bronchogenic carcinoma.

The superior segments of the lower lobes (Fig. 4) are shown as solid densities capping the domes of the lower lobes. On the right the disease is tuberculous pneumonia; on the left, aspiration pneumonia with lung abscess. The overlap of segments of all three lobes in this area usually makes the lateral view necessary for identification.

Anterior basal segment consolidations (anterior-

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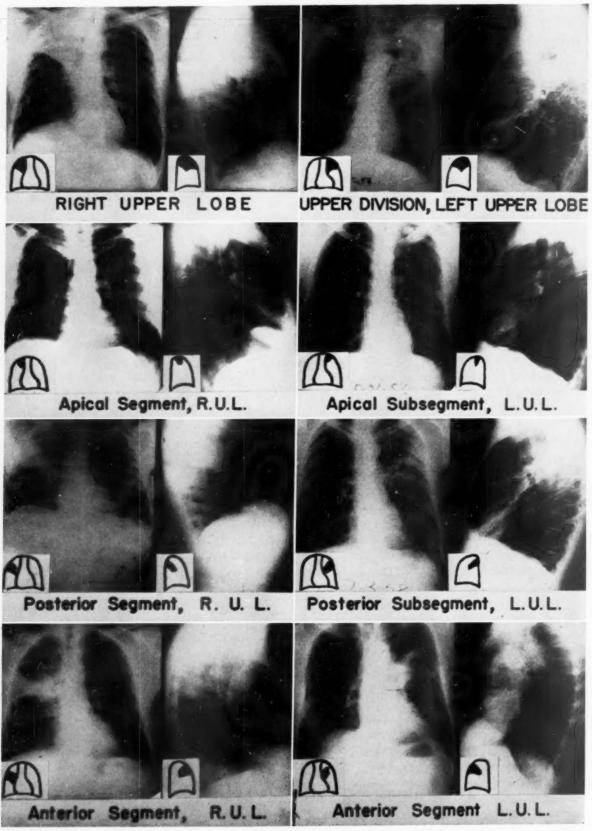


Fig. 2. Segmental consolidations of the upper lobes.

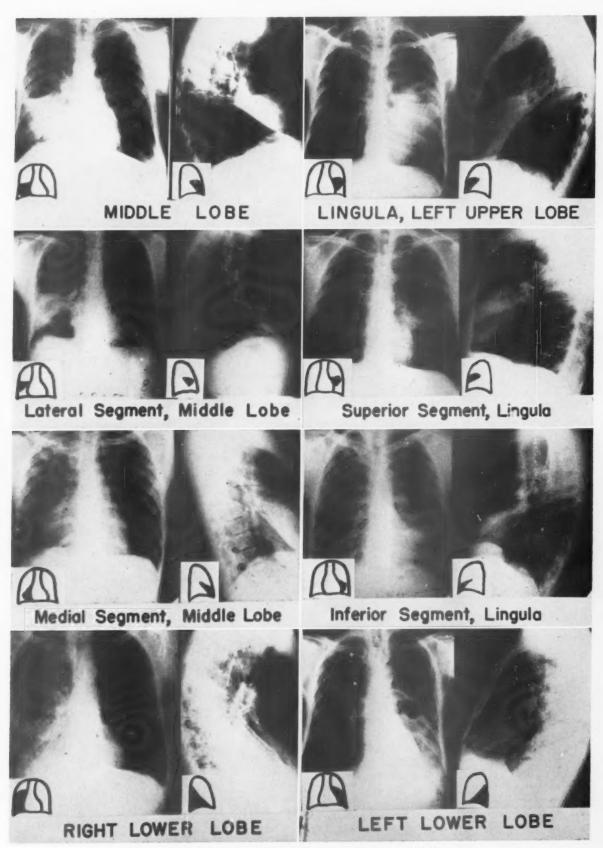


Fig. 3. Segmental consolidations of the middle lobe and lingula.

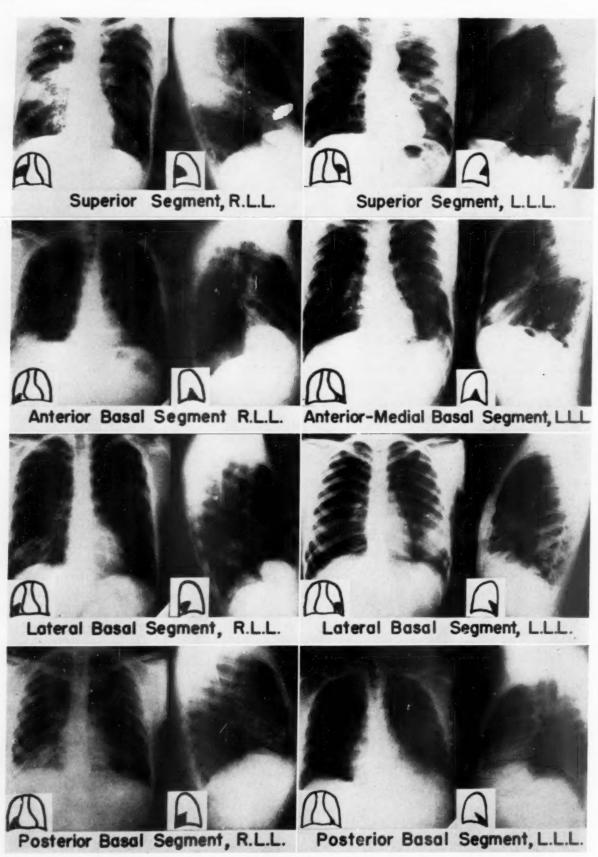


Fig. 4. Segmental consolidations of the lower lobes.

medial basal on the left), (Fig. 4) are diamond shaped, with one end filling the costophrenic angle and the other end extending toward the inferior portions of the hila. On the lateral view the consolidated segment forms a triangular density surmounting the middle of the diaphragm just posterior to the major fissure. When completely consolidated, and especially when partially collapsed, these segments may be confused with interlobar effusions. However, effusions cast fusiform shadows whereas at least one border of a collapsed segment will be concave or straight [13]. These instances are examples of primary atypical pneumonia as are all the basal segmental lesions in our group.

Lateral basal segment (Fig. 4) consolidations cast shadows which are not distinguishable from anterior basal segments on frontal projections or from posterior basal segments on lateral projections. However, on frontal view they often extend a little higher and tend to spare the costophrenic angle more than the anterior basal consolidations.

Posterior basal segments (Fig. 4) when diseased produce large opacities which are nearly identical with those of the lateral basal segments on lateral films. On the right on frontal films the segment overlaps the middle lobe and the medial basal segment. On the left it is almost completely obscured by the heart and occasionally it is completely so. This is the hidden segment of the lung. In our example only the slight haziness at the left cardiac border suggests what is shown on the lateral to be almost complete consolidation of this large segment. Occasionally this shadow may be seen through the heart shadow on frontal films. One should be aware that when the entire lower lobe collapses it may resemble the consolidated posterior basal segment. Preservation of the major fissures or absence of the usual signs of massive loss of lung volume should ordinarily make the distinction possible. The "silhouette sign" is well shown here.

The medial basal segment (Fig. 5) when consolidated produces a hazy infiltration seen at the right cardiophrenic angle obscuring the cardiac border again in accordance with the "silhouette sign." Location of the density in the mid-portion of the diaphragm behind the major fissure on the lateral film serves to distinguish it. On the lateral view this segment appears similar to the anterior basal segment and there is the same necessity to rule out interlobar effusion.

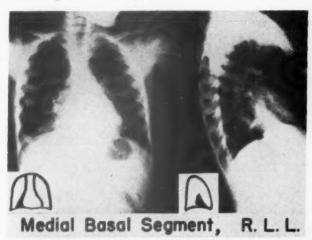


Fig. 5. Consolidation of the medial basal segment.

SUMMARY

A brief review of the fundamental knowledge of segmental consolidations of the lungs has been attempted. This has included historic, pathologic and roentgenographic aspects, as well as a discussion of the more significant anomalies of the bronchopulmonary segments.

The significance of segmental anatomy of the lung in diagnosis is stressed. The value of the "segmental approach" for better understanding the pathogenesis of lung disease and enhancing the significance of written description of roent-genograms is emphasized. In addition, its importance in differential diagnosis is discussed, with analysis of the segmental localization of abscess, bacterial pneumonia, bronchiectasis, viral pneumonias, carcinoma, infarction and tuberculosis.

Finally, the roentgenographic appearance of the consolidated segments on frontal and lateral projections is demonstrated diagrammatically and by roentgenograms of individually consolidated lobes and segments.

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Clinicopathologic Conference

Chronic Alcoholism, Fatty Liver and Sudden Death

S TENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

This fifty-three year old white male accountant entered Barnes Hospital on February 2, 1960 with the chief complaint of "confusion and heavy drinking."

In the seven years before admission, the patient consumed increasing quantities of alcoholic beverages. His intake was one-fifth gallon of whisky daily when unemployed, which was his usual status. Up until three months before admission he ate at least two meals daily, with ingestion of eggs, meat, and fresh vegetables. In the three months before admission he reduced his intake to two then to one meal daily. He ate only small quantities of food during this period. Two months before admission he had an episode of fearfulness and "shakes." On the day of admission, he noted a dry cough; he became nauseated and retched, but did not vomit. He became hyperactive, confused, and gave inappropriate responses to questions. He appeared wide eyed, flushed, and tremulous to the members of the family. He fell to the floor shaking but did not lose consciousness.

There was no history of jaundice, trauma to the head, gastrointestinal bleeding, or exposure to hepatotoxins (other than alcohol).

Nine years before admission he was told that his blood pressure was elevated; he was given pills and instructed to reduce the salt in his diet. He had worn a truss for bilateral inguinal hernias for years. His father was about forty years of age when he died in a mental institution. The cause of death or reason for hospitalization were not known.

Physical examination revealed the following: The temperature was 38.7°c., pulse 100 per minute, blood pressure 180/70 mm. Hg, and respirations 18 per minute.

He was an apprehensive, sweating man with

gross tremor of the hands. He was disoriented as to person and exhibited poor memory and poor judgment. There was no fetor. Icterus could not be detected. The skin was warm and flushed. There was a scaly erythematous eruption of the scalp; a single spider angioma was seen in the right supraclavicular area. There was hair on the chest. Examination of head, eyes, ears, nose and throat was within normal limits. The lungs were clear to auscultation and percussion. The abdomen was slightly distended and exhibited shifting dullness, but no fluid wave. The liver was firm and non-tender; the liver edge descended 10 cm. below the right costal margin. The tip of the spleen was felt 4 cm. below the left costal margin. There were bilateral inguinal hernias. There was decreased sensation to pinprick and vibration below the knees.

Laboratory data were as follows: The red blood cell count was 4 million per cu. mm., the hemoglobin 11.5 gm. per cent, the hematocrit 35 per cent. The red blood cell indices were normal. The white blood cell count was 11,800 per cu. mm. with 4 per cent band forms, 80 per cent segmented forms, 9 per cent lymphocytes, and 7 per cent monocytes. The number of platelets appeared adequate on the stained blood smear. The urine had pH of 6.5, 2 plus protein, no bile or sugar. Occasional granular casts and white blood cells were seen. Two subsequent urinalyses contained a trace of protein. Two stools gave a negative reaction with guaiac. Results of blood cardiolipin were negative.

The blood urea nitrogen was 20 mg. per cent, fasting blood sugar 126 mg. per cent, total serum proteins 7 gm. per cent with 4.8 gm. per cent albumin and 2.2 gm. per cent globulin, total bilirubin 3.1 mg. per cent with 2.4 mg. per cent indirect reacting and 0.7 direct reacting,

alkaline phosphatase 6 Bodansky units. The uric acid was 5.7 mg. per cent, bromsulphalein retention at 45 minutes was 28.5 per cent. Cephalin flocculation, oxaloacetic and pyruvic transaminases, thymol turbidity, protein bound iodine, calcium, phosphorus, acid phosphatase had normal results. Results of direct and indirect Coombs' tests were negative.

A blood culture was sterile; a stool culture contained no pathogens; a culture of clean voided urine had 500 colonies of Staphylococcus albus per ml. Results of skin testing with first

strength PPD were negative.

A roentgenogram of the chest was interpreted as showing fibrocalcific tuberculosis in the left upper lobe of the lung. An electrocardiogram was believed to be compatible with left ventricular enlargement. The Q-T interval was .44 seconds with heart rate of 92. To the interpreter, this finding was suggestive of hypocalcemia.

On admission paraldehyde was given and intravenous glucose solution with vitamins administered. He became less tremulous and rested well. The temperature remained elevated to 38.2 to 39°c. In the hospital he became calm, was cooperative, and ate well. The temperature continued to hover between 38° and 39°c.; no localizing signs or symptoms were detected on repeated examinations. His white blood count on the eighth hospital day was 19,600 per cu. mm. with 69 per cent segmented forms, 15 per cent lymphocytes, and 16 per cent monocytes. On this day he had a syncopal episode and fell to the floor. Examination immediately after this episode was within normal limits. One hour later he had a generalized convulsion and became cyanotic. No cardiac action could be detected. He did not respond to the administration of intracardiac adrenalin and artificial respiration.

CLINICAL DISCUSSION

DR. Sol Sherry: The case discussed today involves a fifty-three year old white male who was a chronic alcoholic; he drank very seriously in the three months before admission, and progressively eliminated other sources of calories and nutrition. Two months before admission he had an episode of fearfulness and shakes. On the day of admission he suddenly became agitated, confused, tremulous, and appeared to have a convulsion, although this is not specifically stated. Abnormal findings on physical examina-

tion included fever, pulsus alternans, and enlarged, firm, non-tender liver, a palpable spleen, and some peripheral sensory loss below the knees. Laboratory examination revealed a moderately elevated serum bilirubin, both direct and indirect, abnormal bromsulphalein retention, and a slightly elevated alkaline phosphatase. The rest of the tests of hepatic function gave normal results.

The patient improved on a regimen consisting of sedation, and the parenteral administration of glucose and vitamins. However, he continued to have a low grade fever. On the eighth hospital day he suffered a syncopal attack from which he quickly recovered. However, one hour later he had a generalized convulsion, was found to be pulseless, and died shortly thereafter. Dr. Brown, was there active disease in the upper lobes of the lungs?

DR. MARK BROWN: I can't make a definite statement, but I personally doubt active disease from the available roentgenograms.

DR. SHERRY: Dr. Karl, I wonder if you might give us your interpretation of the nature of hepatic disease in this man.

Dr. MICHAEL M. KARL: I think that the evidence available, Dr. Sherry, would indicate that this patient probably had an alcoholic fatty liver. He had a history of excessive intake of alcohol associated with a rather meagre nutritional intake at the same time. He had hepatomegaly which by description would fulfill the characteristics of fatty alcoholic liver. His spleen was palpable. The abnormal results of liver function tests consisted of bromsulphalein retention above and beyond what would be expected on the basis of fever alone, and an elevated serum bilirubin, without much impairment of other liver functions. These findings are consistent with the fatty liver of alcoholism.

Dr. Sherry: Can we account for the moderate fever, the mild leukocytosis, and the splenomegaly on the basis of a fatty liver alone, without invoking, say, active cirrhosis?

DR. KARL: I think we can. There are several possible explanations for these. Fatty liver itself, without any other subsequent findings at autopsy, has been associated with fever and leukocytosis. In addition, fatty liver seems to predispose to other hepatic injuries, such as necrosis. The fact that the patient did not have an elevated transaminase would make me feel that necrosis as a sole explanation for this fever is not too satisfactory. Lastly, patients with fatty

livers are very prone to other infections, especially non-specific respiratory infections, tuberculosis, which has been suggested by the roentgenogram of the chest.

DR. SHERRY: I would agree completely with this interpretation, that the most likely diagnosis is that this man had a very large, fatty liver, associated with his alcoholism and malnutrition. I think some recent observations by Lieber and Schmid which are of considerable interest suggest that in addition to the known factors involved in the production of a fatty liver, that alcohol may have a somewhat more direct action. I wonder, Dr. Recant, if you could comment on their studies?

DR. LILLIAN RECANT: Lieber et al.* recently reported studies concerning the effect of alcohol on the experimental production of fatty livers. They demonstrated that in animals in which alcohol was given by stomach tube a net increase in liver fat would develop within sixteen hours when compared with control animals fed isocaloric amounts of glucose.

In attempting to assess the mechanism by which alcohol produced this effect, the following questions were raised: is there increased mobilization of fatty acids and fat from adipose tissue to the liver? Is there decreased mobilization of fat from the liver? Is there an increase in the synthesis of liver fat or a decrease in breakdown? In an attempt to answer these questions they carried out the following studies.

By administering C¹⁴-acetate to rats on normal diets, the specific activities of liver and adipose tissue fat were described over a five day period and found to differ in a characteristic pattern. If the administration of ethanol increased mobilization of fat to the liver, the specific activities of liver fat after ethanol should approach that of adipose tissue. This did not prove to be the case.

In dealing with the second possibility, namely decreased mobilization of fat from liver, ethanol was given to rats and within sixteen hours a tracer dose of C¹⁴-acetate. In these studies the liver contained greater quantities of fat with a higher specific activity than liver fat in controls. If there had been decreased mobilization of fat from the liver, the specific activity would certainly not have been higher, and might actually

It can be concluded from these studies: (1) that alcohol per se induced a fatty liver in animals; (2) that the mechanism involved appears to be an enhanced synthesis of fat related to the formation of DPNH; and (3) there are many questions which remain to be answered, particularly as they relate to fatty livers in human subjects.

DR. SHERRY: Thank you very much. Dr. Hartroft and his group here in the Department of Pathology are recognized as world authorities on the subject of fatty liver. Dr. Grisham would you tell us of your observations and of some of the recent experimental advances in the production of fatty liver.

DR. Joe W. Grisham: In man and most experimental animals, between 2 and 5 per cent of the wet weight of the liver is lipid. Under normal conditions this lipid is not stainable by Oil red O and therefore is not visible in microscopic sections. An increase in the lipid content of the liver above the 2 to 5 per cent level is

have been lower. These data also pointed to increased synthesis of fat as a major possibility.

It was further shown that liver slices but not adipose tissue slices could metabolize tracer amounts of alcohol and that addition of alcohol to liver slices enhanced C14-acetate incorporation into fat, but did not do so in adipose tissue. Lieber and Schmid concluded that tissue metabolism of alcohol was related to the increase in liver fat. The enzyme alcohol dehydrogenase, known to be present in liver, converts alcohol to acetaldehyde with the reduction of DPN. Further oxidation of acetaldehyde results in more reduced DPN. In essence, then, a twocarbon molecule is responsible for the production of two moles or more of reduced DPN. In contrast, glucose, a six carbon molecule, is relatively less effective in production of reduced DPN. Since the synthesis of fatty acids is a reductive synthesis and requires reduced nucleotides (TPN or DPN), Lieber and Schmid surmized that production of reduced co-enzyme within liver following the administration of alcohol was responsible for the acceleration of fat synthesis. The use of a sorbitol-fructose system capable of generating reduced DPN also resulted in vitro in accelerated synthesis of liver fat. Finally, methylene blue, which is a hydrogen acceptor, partially inhibited the alcohol effect on the synthesis of fat. In additional experiments no evidence for a decreased rate of liver fat oxidation could be found.

^{*} LIEBER, CHARLES S., DECARLI, LEONORE M. and Schmid, R. Stimulation of hepatic fatty acid synthesis by ethanol in vivo and in vitro. J. Clin. Invest., 39: 1007, 1960.

associated with the development of stainability. For small increases in hepatic lipid, estimation by microscopic methods is probably more sensitive than by biochemical technics because of the frequently focal nature of cellular accumulation. Dilution of a few fat-filled cells by many normal ones will mask the extent of the change on affected portions when the usual chemical technics are employed. Any liver that contains stainable fat is, by definition, a fatty liver, but there are wide ranges of the amount, type, and

location of the lipid.

In order to understand how the development of fatty liver comes about, the function of the liver in the metabolism of fat must be considered. This organ is the chief site of fatty acid, cholesterol, phospholipid and lipoprotein synthesis. It is also the major site of degradation of fatty acids of dietary and depot origin. There are several factors that influence the amount of lipid in the liver, and an imbalance of these results in increased lipid and the appearance of stainable fat. Factors that tend to increase hepatic lipid are: (1) the synthesis of fatty acids in the liver from carbohydrate and protein; (2) the influx of dietary lipid, much of which passes through the liver prior to being deposited in fat depots; and (3) the mobilization of fat to the liver from fat depots. Factors that normally tend to decrease hepatic lipid are: (1) mobilization of fat from the liver; (2) passage of cholesterol and phospholipids into the blood; and (3) the oxidation of fatty acids in the liver. In essence, most examples of fatty liver depend on one or more of the following factors: (1) increased dietary intake; (2) increased hepatic synthesis; (3) decreased hepatic oxidation; (4) decreased mobilization from the liver; and (5) increased mobilization from fat depots to the liver.

It is probably infrequent that one of these factors acting alone is responsible for hepatic liposis. Increased dietary intake, if great enough, in the form of either lipid or calories will result in fatty liver. Decreased hepatic oxidation apparently occurs in choline deficiency in experimental animals. Also in lipotropic deficiencies in animals there may be a decreased mobilization of fat from the liver. Lipid mobilization is poorly understood and the relation of alterations in phospholipid synthesis to mobilization is a vexing question. At the present time it cannot be stated what part decreased hepatic mobilization plays in the occurrence of hypolipotropic fatty livers. It is

becoming apparent, as Dr. Recant just pointed out, that the intake of alcohol results in an increased hepatic synthesis of fatty acids without a comparable elevation in the rate of hepatic oxidation or mobilization. In this way, the fatty liver associated with intake of alcohol differs from that caused by lipotropic deficiency. These differences may well have therapeutic import. If an increase in the synthesis of fatty acids is the essential cause of the alcoholic fatty liver, then supplementation of the diet with lipotropic factors to reduce the level of fat would not be expected. However, as was mentioned previously, it is unlikely that any one single enzymatic abnormality is responsible for any case of fatty liver and the latter probably results from a combination of factors working together or against each other. Under optimal conditions choline supplementation of the diet will reduce the degree of hepatic liposis in a rat receiving alcohol over a period of several weeks or more. Increased transport of fat to the liver is thought to be responsible for a large number of fatty livers in both man and experimental animals. Fat mobilization from peripheral depots is subject to the influence of several hormones. The fatty liver of most debilitating diseases is thought to be brought about through the pituitaryadrenal axis. In the experimental animals, the fatty liver resulting from the ingestion of carbon tetrachloride is probably the result of increased peripheral mobilization stimulated by epinephrine.

From a morphologic standpoint, the site of initial fatty metamorphosis can be rather clearly divided into periportal (Fig. 1) and centrolobular (Fig. 2) regions of the hepatic lobule. These localizations have some etiologic implications. Periportal lipid is associated with deficiencies of amino acids, of protein and also with hyperphagia and hyperalimentation. Accumulations of stainable fat in the centrolobular regions of the hepatic lobule are more typically associated with lipotropic deficiency and the constant ingestion of alcohol. The exact reasons for this differentiation in localization are not known, but we do know that the liver lobule is not an homogeneous structure, from either cytomorphologic or enzymatic standpoints. Since the levels of different enzymes vary quite widely from the periportal to the centrolobular regions of the hepatic lobule it is reasonable to assume that the differences in localization of fat may reflect alterations in activities of different

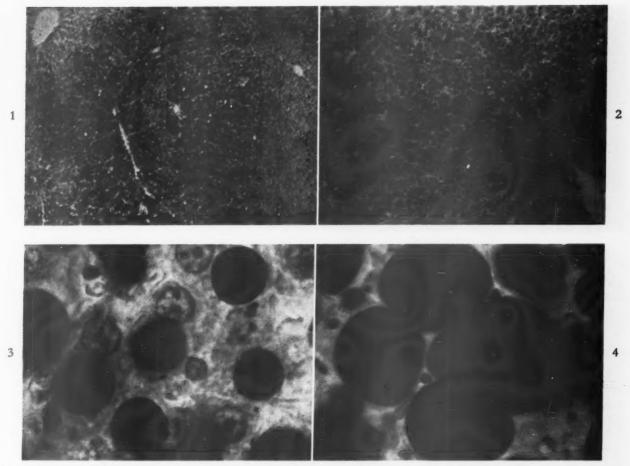


Fig. 1. Periportal localization of fat in the hepatic lobule of a hyperphagic rat. Frozen section. Oil red O-hematoxylin stain, \times 150.

Fig. 2. Centrolobular localization of fat in the liver of a rat fed a choline-deficient diet for two days. Frozen section. Oil red O-hematoxylin stain, \times 150.

Fig. 3. Large droplets of fat which fill the cytoplasm of single hepatocytes. From a rat fed a choline-deficient diet for two weeks. Oil red O-hematoxylin stain, × 1,000.

Fig. 4. Illustration of the manner of formation of a fatty cyst by coalescence of fat in several hepatocytes. Rupture of the thin cytoplasmic strands separating the fat in adjacent cells allows it to become extracellular. The wall of the cyst will be formed of all the cells in this group which originally contained fat within their cytoplasm. From a rat fed a choline-deficient diet for one month. Oil red O-hematoxylin stain, $\times 1,000$.

enzymes. If the accumulation of fat is great enough, the lobular differential is lost and stainable fat may accumulate throughout the entire lobule. In this case, one is unable to make etiologic deductions from fat localization.

We attach some import to the form of the fat within the hepatocyte. For instance, most of the lipotropic deficiencies and alcoholic intoxications are associated initially with small droplets of intracytoplasmic stainable lipid which adjoin to fill the cell (Fig. 3) and then, by coalescence of several fat-filled cells, form large fat-filled cysts. (Fig. 4.) In the latter, the walls of the cysts are composed of many hepatocytes and the fat is actually extracellular. In many of the other

conditions described the fat remains in small droplets in the cytoplasm of the hepatocyte (Fig. 5), even in instances in which the total amount of lipid may be as great as it is in the other cases associated with the formation of fatty cysts. Again, the reason for this difference is not clear, but it does exist.

Biochemists have demonstrated that with the hepatocyte there are separate enzyme systems concerned with the oxidation and with the synthesis of fatty acids. The oxidizing system is located in or on the mitochondrial fraction, whereas the synthesizing system is associated with the soluble or supernatant fraction. (Fig. 6.) Apparently neither of the systems carry out the

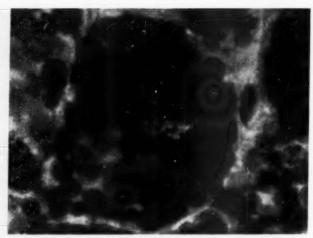


Fig. 5. An hepatocyte whose cytoplasm is stuffed with many discrete droplets of fat. Each droplet is separated from its neighbor by delicate cytoplasmic septa. Even with marked accumulations of lipid in the liver the fat in individual hepatocytes remains in droplet form and fatty cysts rarely form. From a rat with hyperphagia. Oil red O-hematoxylin, \times 1,000.

reverse reaction. Because of their separate localizations it is conceivable that specific factors could affect one and not the other. This concept agrees with what we see by electron microscopy. We believe that, in general, the fatty livers of different etiologic types can be divided into two broad groups (1) those associated with mitochondrial abnormalities, and (2) those in which the mitochondria remain morphologically normal and in which some abnormalities in other cytoplasmic organelles occur. For instance, experimental choline deficiency causes a morphologic abnormality of mitochondria characterized by an apparent tendency to ensphere and enlarge. (Fig. 7.) This occurs rapidly when choline is excluded from the diet and is quickly repaired when it is replaced. (Fig. 8.) Choline is important for maintaining mitochondrial integrity in hepatocytes and the disruption of structure of mitochondria in the deficiency of choline may be associated with impairment of action of the enzymes therein localized (fatty acid oxidation). Essential deficiency of fatty acid results in a somewhat similar lesion.

In some other types of fatty liver the mitochondria do not become abnormal as abruptly as in choline deficiency. Usually, this type of change is associated with the small droplet type of lipid accumulation. For example, in chronic ethionine intoxication, variable amounts of lipid accumulate in the liver. In this instance, the mitochondria are not grossly altered morphologically (Fig. 9), but there are significant changes in the endoplasmic reticulum. A similar relationship exists in the cholesterol fatty liver and the liver of hyperphagic animals. We have not yet studied the morphologic changes in chronic alcohol feeding.

The conclusion to be drawn from this discussion is that there are a myriad of causes of hepatic liposis. However, a beginning is being made in determining the initial locus of action in relation to cellular organelles and enzyme systems primarily affected by each agent.

DR. SHERRY: Dr. Hartroft would you make some comments now? I'll show the pathologic data later.

DR. W. STANLEY HARTROFT: There are one or two things in connection with the discussion I would like to underline. As you can see, biochemical studies do not help us differentiate the various kinds of fatty livers. We can, however, differentiate some of them by light microscopy, according to the position of the fat within the lobule and the form of droplets within cells. The electron microscope takes us even further. It appears that fatty livers associated with decreased oxidation of lipid may be associated with enlargement of mitochondria, although future work is needed to establish this observation. Surgical pathologists have told us that only one cell is needed for a diagnosis, and it may be that some day by electron microscopy only one mitochondrion will be needed. Recent studies during the last three or four years have brought us back to some extent to the concepts of Virchow, who first introduced the terms fatty degeneration versus fatty infiltration, although in the past I have decried the use of these terms in relation to fatty livers. Virchow believed that fatty degeneration was indicated by small droplets of fat and that fatty infiltration was indicated by large spheres of fat within parenchymal cells. We maintained that droplet size was probably a matter of degree; that when small droplets became numerous enough they would fuse to form large spheres. This sequence is true for choline deficiency, but as you have seen, it is not true for some of the other forms of fatty liver that have been discussed. There is a distinct difference in this respect with regard to the etiology of fatty liver and despite our original views we have come back to look at the size of the droplets in relation to the total amount of fat. Regardless of the amount of fat that accumulates within a single liver cell following hyperphagia, the

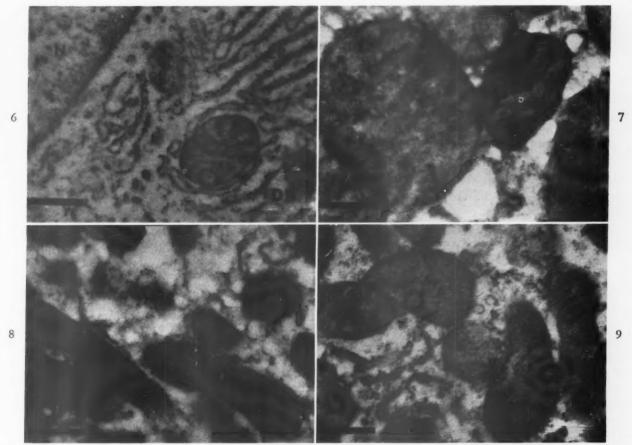


Fig. 6. An electron micrograph of a portion of a normal hepatocyte from the liver of a rat fed a choline-supplemented diet. A portion of the nucleus (N), a mitochondion (M), dense body (DB), and strands of endoplasmic reticulum (ER) are shown. The bar represents about 0.5 micron, \times 40,000.

Fig. 7. An electron micrograph of mitochondria from the liver of a rat fed a choline-deficient diet for three months. Notice the greatly increased diameter (compare with Fig. 6) and the derangement of inner structure. The bar represents about 0.5 micron, \times 40,000.

Fig. 8. An electron micrograph of mitochondria from the liver of a rat fed a choline-deficient diet for three months and then fed a choline-supplemented diet for two days prior to killing. Note that the size of these mitochondria is about the same as are those in liver of the control rat. Choline supplementation results in rapid return of the ensphered mitochondria to the normal shape. The bar represents about 0.5 micron, \times 40,000.

Fig. 9. An electron micrograph of mitochondria from the liver of a rat fed an ethionine-supplemented diet for two months. These mitochondria do not differ significantly from those in the liver of the normal rat. The bar represents about 0.5 micron, $\times 40,000$.

droplets will always remain discretely separated by little intracytoplasmic septa, although the cell will enlarge tremendously. These cytologic changes help to distinguish the fatty livers of hyperphagia from those of choline deficiency.

The ability of liver cells to regenerate is well known. If part of one lobule is destroyed, another portion will enlarge. I think the evidence in Dr. Grisham's electromicrographs suggests that this principle may not only be limited to one cell replacing another dead or injured cell, but also may apply to different portions of a single cell. The evidence is not

complete yet, but suggests that if one mitochondrion is destroyed, another may form within the same cell to take its place. Therefore, within the same cell we may have degeneration and regeneration of intracytoplasmic organelles going on at one and the same time. The remarkable ability of the liver to regenerate is an observation centuries old, but we are still finding new evidence of its extent.

DR. SHERRY: Thank you. I think it is really exciting to see how the whole problem of fatty livers is opening up again. We are beginning to recognize that there are different mechanisms

which operate, and perhaps the electron microscope will give us a much better understanding of these mechanisms. In addition, it seems that in the alcoholic patient with malnutrition, alcoholism may contribute directly as well as via the effects of malnutrition in the development of the very extensive fatty livers seen at postmortem examination.

There are two other aspects I think we should briefly touch on: One deals with the encephalopathy which this man presented; the other, of course, with the terminal episode which caused his death. Dr. Reichlin, would you classify for us the nature of the encephalopathy which this man presented? As you remember, he had two bouts which were a little different. Would you also comment briefly on the present status of

alcoholic encephalopathies? DR. SEYMOUR REICHLIN: This man demonstrated a number of the important mental changes which occur in the life of a chronic alcoholic. The most important problem and the one we know the least about, both in this patient and in alcoholism in general, is the cause of compulsive drinking. Aside from the initiating psychological disease, there are two major kinds of brain disturbance in the alcoholic. One is related to alcohol as a narcotic, and the other is related to the fact that alcoholics suffer from severe nutritional deficiencies. The nutritional deficiency syndromes are not different from those seen in other forms of malnutrition, and the alcoholic manifestations of narcosis are paralleled in the effects of other necrotizing substances. An excellent classification of the alcoholic syndromes has been given by Victor and Adams* based on experience at Boston City Hospital. The most common disorder is acute drunkenness, the manifestations of which are generally familiar.

Patients who have been on a spree or on a series of sprees may have alcoholic tremulousness which appears to be a mild abstinence syndrome precipitated by a period of sleep in which no alcohol has been taken. The well-known drink before breakfast relieves the tremor and the anxiety symptoms. In more extreme cases of withdrawal, alcoholic hallucinosis, psychosis, and delerium tremens in its fully developed form may be manifest. Identical symptoms of tremulousness, anxiety, anorexia, nausea, and

* VICTOR, M. and ADAMS, R. D. The effect of alcohol on the nervous system. Res. Publ. A. Nerv. & Ment. Dis., 32: 526, 1953.

vomiting are seen in barbiturate withdrawal or in experimental withdrawal from alcohol addiction. The episodes of tremulousness that occured in this patient before admission was probably a mild abstinence reaction. The patients with chronic alcoholism who have delerium tremons are severely addicted and their illness is precipitated by withdrawal or by complicating medical disease. Occasionally "DT's" may begin even while the patient is drinking; in these cases there is a possibility that the patient is not consuming or absorbing enough alcohol to satisfy his extreme requirements. One of the interesting features of alcoholic hallucinations is that they are chiefly auditory, and then when they are visual, the forms observed are small, bizarre and frightening. In addition to the illnesses mentioned, "rum fits" are another manifestation of alcohol withdrawal. These usually occur within forty-eight hours after hospital admission.

The second important category in disturbance of the nervous system in alcoholics are the nutritional deficiencies. These include neuropathy, Wernicke's disease and Korsakoff's syndrome; all are caused by thiamine deficiency, not by any "toxic" effects of alcohol. The Korsakoff's syndrome embodies a peculiar defect in memory in which the patient supplies missing information by confabulation. It may be regarded as the irreversible end stage of treated thiamine deficiency encephalopathy of which Wernicke's disease with its cranial nerve signs is the active form. Recently the importance of damage to the mammillary body and the periventricular gray substance of the third ventricle has been emphasized and we would be interested to see whether or not the patient had this abnormality. Incidently, both niacin and pyridoxine deficiencies have been seen in alcoholics, and may contribute to the manifestations of the illness. In this patient the presence of neuropathy suggests thiamine deficiency, but the lack of oculomotor signs tends to exclude Wernicke's disease. One of the difficult features in this case is the syncopal attack and convulsions which preceded his unexpected death. Although sudden, unexplained death is common in "DT's", the protocol gives no data to support this diagnosis. Also, his convulsion occurred so much later in the course of hospitalization than is usual for rum fits that other causes should be carefully considered.

DR. SHERRY: Actually, I thought this man

probably did have a bout of alcoholic tremulousness about two months before admission and then at the time that he came in, that he probably had a recurrence of this plus a rum fit. Do you think this is reasonable? I notice that he didn't really have a history of abstinence, but I think before he actually came into the hospital he may have temporarily abstained from drinking.

DR. REICHLIN: I agree with your point about tremulousness, but I am not sure about the fits. The timing of the fit is important, because rum fits occur in the phase of acute withdrawal. There is one other point I would like to mention. In a recent study* cerebral fat emboli were found in patients who had died suddenly while suffering from delerium tremens; perhaps this was the cause of death in this patient.

DR. SHERRY: I think this brings us up to the last point which we can touch on very briefly, and that is, Dr. Karl, what do you think was the final cause of death in this patient? As you recall, he was doing well and then on the eighth day he had a syncopal attack. He recovered and then he had a convulsion and was found to be pulseless. He died despite emergency measures to resuscitate him. Do you think that fat embolization has to be seriously considered here?

DR. KARL: As Dr. Reichlin has indicated, the majority of the patients of this type who die suddenly have nothing other than fatty livers demonstrable at autopsy. Occasionally, acute pancreatitis is present. We have no enzyme values to suggest this complication. Two other points, both of which have been reported experimentally by Dr. Hartroft, might remotely explain some of these sudden deaths. Dr. Hartroft has demonstrated that animals on a choline deficient diet who have been fed salts of lauric acid demonstrate fatty infiltration of the myocardium, † and I note that Dr. Popper, in his discussion of this study, states that he sees similar lesions in the myocardium of alcoholics at autopsy. If this occurs clinically, we have failed to recognize it. Secondly, Dr. Hartroft has reported that fat may escape into the circulation from the kind of fatty cysts that Dr. Grisham demonstrated, and may cause pulmonary

embolism. Durlacher* reported massive fatty pulmonary embolizations in five of twenty-five patients of this sort, extensive enough to explain sudden death.

DR. SHERRY: We will now turn the discussion over to Dr. Grisham who will present the pathologic data. Our final diagnosis is: Chronic alcoholism, fatty liver, and alcoholic encepalopathy. We shall be interested to find out what the terminal event was which caused death.

PATHOLOGIC DISCUSSION

DR. GRISHAM: This patient's pathologic disorders would seem from the discussion to involve mainly his liver and his brain. His liver was, indeed, fatty. It weighed 2,900 gm., was tan in color, soft in consistency and greasy on cut section. Frozen sections stained for fat demonstrated marked accumulation of lipid, especially in the centrolobular regions. Fatty cysts were numerous. The fat in sections had a somewhat "motheaten" appearance and this we tend to associate with fat resorption. Perhaps the fact that his intake of alcohol had been stopped and that he was being actively treated with B vitamins is important in this regard. In the centrolobular areas there were areas of fibrosis and active necrosis. The latter may help explain the hyperpyraxia. No two central areas were connected by fibrous tracts, however. The parenchyma adjacent to portal spaces was largely of plates two cells thick indicating regeneration. There is some evidence of impaired hepatic function over a long period of time. The testes were atrophic, spermatogenesis was almost completely suppressed and many seminiferous tubules were virtually completely hyalinized. Levdig cells were prominent.

There was no visible morphologic lesion of the brain to explain his death. The brain, which weighed 1,300 gm., was not edematous. Certain clinical aspects would be consistent with Wernicke's hemorrhagic leukoencephalopathy, but the lesions were not present. Fat emboli were present neither in the brain nor in the lungs or kidneys. In many instances of alcoholic encephalopathy histologic lesions of the brain are not visible. Clinically, I think there is no doubt that he did have an alcoholic encephalopathy. Sections of femoral nerve showed normal myelinization.

^{*} Durlacher, S. H. et al. Sudden death due to pulmonary fat embolism in persons with alcoholic fatty livers. Am. J. Path., 30: 633, 1954.

^{*} Lynch, M. J. G., Raphael, S. S. and Dixon, T. P. Fat embolism in chronic alcoholism. *Arch. Path.*, 67: 68, 1959.

[†] HARTROFT, W. S. Liver Injury, 12th Conference. Josiah Macy, Jr. Foundation. New York, 1953.

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The lungs, which weighed 1,300 gm. together, were markedly congested and edematous. The alveoli were filled with homogeneous, eosinophilic material. This was an apparently acutely developing edema. Myocardial function clinically was good. At autopsy the heart was within the range of normal. There was no fatty degeneration of the myocardium. Not infrequently, acute pulmonary edema is a sequelae of generalized convulsions and often is the precipitating cause of death. The spleen and the liver were

also congested. The kidneys were somewhat pale, but showed only moderate arteriolosclerosis.

Our primary anatomical diagnoses are: Fatty metamorphosis of the liver with diffuse centrolobular necrosis and fibrosis; congestion and edema of the lungs, advanced; congestion of the spleen and liver; and congestion of the vessels in the white matter of the brain.

Dr. Sherry: There was nothing to suggest acute beri-beri?

DR. GRISHAM: No.

Carcinoid Syndrome Associated with Hyperserotoninemia and Normal 5-Hydroxyindoleacetic Acid Excretion*

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CINCE the recognition of the association of excessive production of 5-hydroxytryptamine (serotonin) by metastatic carcinoid tumors with the various manifestations of the carcinoid syndrome, the determination of urinary 5hydroxyindoleacetic acid (5-HIAA) has been widely used for diagnostic purposes. The excretion of 5-HIAA has been found to be elevated in the vast majority of cases, but occasional transitory drops in output to normal levels have been recorded, making repeated determinations advisable in cases of suspected carcinoid syndrome with normal 5-HIAA excretion [1]. This paper describes a patient with a metastatic carcinoid tumor who had hyperserotoninemia, but no elevation of urinary 5-hydroxyindoleacetic acid during an eightmonth period of study, despite a history of flushing attacks of three years' duration.§

CASE REPORT

A twenty-five year old unmarried white woman was seen for the first time at the University of Minnesota Hospitals in March 1955, when she was admitted to the orthopedic and physical medicine services for the treatment of scoliosis, flexion deformities of the hips and knees, and shortening of the heel cords, caused by poliomyelitis in 1946. General physical examination at that time showed no other abnormalities, and her hemoglobin was 14.8 gm. per cent. When seen in December 1955, however, she was found to be anemic, with a hemoglobin of 9.4 gm. per cent and a serum

iron of 32 μ g. per cent. The stool guaiac test was 4 plus on a meat-free diet. At that time proctoscopy, upper gastrointestinal series and a barium enema were non-contributory. The patient's hemoglobin rapidly returned to normal after two months of ferrous sulfate therapy, and remained at normal levels. Further stool guaiac determinations were not made.

In September 1957 the patient was readmitted for a tendon transplantation; following administration of penicillin and a blood transfusion, facial erythema and periorbital edema developed. At that time she experienced "intermittent body rashes which disappear after a few minutes." The periorbital edema and erythema subsided within twenty-four hours. In November 1957, one day after another tendon transplantation, nausea, vomiting and crampy abdominal pain without abdominal distention developed. This attack rapidly subsided. One day after a spinal fusion later in November 1957 hypotension and abdominal distention developed, with crampy pain which responded to nasogastric suction.

In September 1958 the patient was admitted for the fourth time to the Division of Orthopedic Surgery for further corrective procedures. At that time the intern noted that the patient had had "red flushes," and suspected carcinoid syndrome. A qualitative test for 5-hydroxyindoles was performed, and the result was negative. The patient was discharged, to be seen again in December 1958 in the outpatient department with complaints of anorexia and a "sore" sensation in the mid-abdomen, unrelated to the ingestion of food, and present for approximately two weeks. At that time a tender, movable, 1 by 5 cm. mass was palpated in the mid-abdomen. An upper gastrointestinal series, with small bowel follow-through, as well as a barium enema, were negative, and she was admitted to the University Hospitals in January 1959

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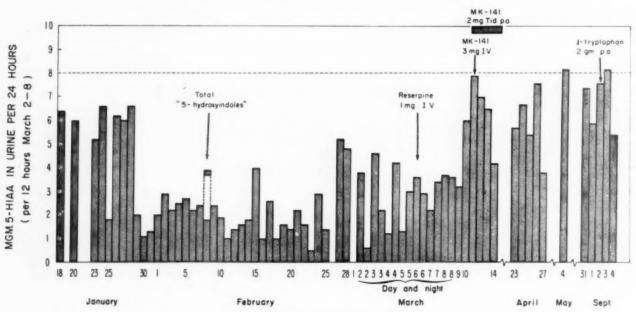


Fig. 1. Urinary 5-HIAA output.

for exploratory laparotomy. She stated that for three weeks prior to admission she had noted no abdominal pain.

On examination her blood pressure was 110/75 mm. Hg and her weight 77 pounds. The residual deformities of the spine and extremities were present. No significant adenopathy was noted. There were no heart murmurs. The liver and spleen were not palpated. The blood urea nitrogen was 16 mg. per cent and the urine specific gravity 1.015 on a random specimen, with no albumin, casts or cellular elements. The creatinine clearance was 143 L./day (normal 168 ± 23 L./day) and phenolsulfonphthalein excretion was 31 per cent in fifteen minutes and 97 per cent in two hours. At operation on January 9 the abdominal mass was found to be an enlarged mesenteric lymph node, which was interpreted as an argentaffinoma on frozen section. A lesion of the terminal ileum, 1.5 cm. in diameter, concave on its mucosal surface, and extending through to the serosa, was identified at operation, and an 8 cm. segment of ileum removed. Numerous small yellow nodules were seen in both lobes of the liver, but none were resected. A Masson's argentaffin stain showed argentophilic granules in the cytoplasm of tumor cells present in the lymph node.

The flushing attacks were unabated after operation. Careful questioning revealed that the patient first had noted attacks of flushing in the summer of 1956, occurring only very occasionally. Subsequently the attacks became more frequent, appearing from one to six times daily. The character of flushing had not changed; flushes frequently were noted in the morning on arising, and lasted one to two minutes. The patient first noted a "warm sensation" of the face which was followed by a diffuse erythematous flush of the face,

and then patchy red blotches which appeared over the trunk. She did not appear cyanotic, and she noted no wheezing, diarrhea, edema, arthralgia or abnormal pigmentation.

The patient was admitted again in April 1959. At that time she had an isolated perfusion of the liver, via the portal vein, with 10 mg. of nitrogen mustard.* One 3 by 3 cm. nodule was removed from the liver for biopsy and chemical analysis. The tissue removed was metastatic carcinoid tissue. The patient subsequently returned to work as a clerk, and has continued to have one to four attacks of flushing daily.

EXPERIMENTAL PROCEDURES

Methods. The patient was maintained on an 1,800 calorie, 70 to 80 gm. protein diet during her hospital stay. Medicaments included Darvon® compound, Seconal® and Tuinal,® as needed during this period. All medicaments were withheld from February 9 to 16. A phenothiazine derivative (Compazine®) was given only in the postoperative period, from April 4 to May 4. Urine 5-HIAA was measured quantitatively by the method of Udenfriend et al. [2] in twenty-fourhour specimens. Total 5-hydroxyindoles were measured in unextracted urine, using the 1-nitroso-2naphthol color reaction with 5-HIAA standards. Creatinine was determined in most specimens. Serum serotonin levels were measured by fluorimetry, after isolation from the serum by the method of Davis [3]. Plasma 5-HIAA, as well as plasma and tumor serotonin values, were estimated by fluorimetry [4]. Urine serotonin was determined by fluorimetry [4] and/or by bioassay [5]. Urinary tryptophan

^{*} Performed by Drs. J. B. Aust and Robert K. Ausman of the Department of Surgery.

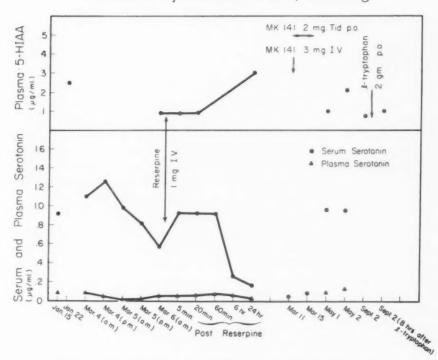


Fig. 2. Serum and plasma serotonin, plasma 5-HIAA levels.

was measured by the xanthoprotein method [6] and urine histamine by the method of Roberts and Adams [7].* Chromatography of the urine was carried out according to the methods of Bumpus and Page [8]. Gastric secretory studies were performed on two twenty-four-hour specimens of gastric juice, the collections being divided into six-hour periods, and analyzed separately for pepsin activity (tyrosine activity/ml.) [9], free acid, pH, and in vitro digestive activity utilizing a bolus of meat [10]. Urine samples were collected by the method of Johnson [11] for catechol amine content, and catechol amine assay was performed by the methods of Sobel and Henry [12], and Johnson. Fifteen microcuries of 5-hydroxytryptamine-3-C14 were given by mouth. Urine then was collected for eight hours, concentrated, extracted with acetone, and the extract chromatographed. Radioactivity was scanned with a chromatogram scanner manufactured by Atomic Accessories, Inc., Bellerose, New York.

Results. The urinary excretion of 5-hydroxy-indoleacetic acid during an eight-month period is shown in Figure 1. The daily output of 5-HIAA varied from 0.5 mg./day to 8.2 mg./day. On March 6, 1.0 mg. of reserpine was given intravenously, and serum and plasma serotonin, as well as plasma and urinary 5-HIAA were determined at intervals thereafter. (Fig. 2.) During the period prior to and following

* Kindly determined by Dr. C. F. Code, Mayo Clinic, Rochester, Minnesota.

TABLE I URINE TRYPTOPHAN LEVELS

Date	Twenty- Four-Hour Output (mg.)	
March 6	178	
March 10	146	
May 4	138	
August 31	89	
September 1	72	
September 2 (2 gm. L-tryptophan orally).	63	
September 3	108	
September 4	58	

reserpine administration, twelve-hour urine aliquots were used for 5-HIAA determination. The patient thereafter was given a short trial of cyproheptadine (MK-141),* a potent antihistaminic and serotonin antagonist, with no striking change in serotonin levels or 5-HIAA output. (Figs. 1 and 2.)

Serotonin levels in serum and plasma are shown in Figure 2. Urine tryptophan levels are recorded in Table I, and were either normal or moderately elevated (normal range 69 ± 25 mg./day) [13]. Acid and peptic activity are

* Furnished by Merck Sharp and Dohme Research Laboratories.

Table II

ACID (MEQ. HCL; NORMAL, 5 TO 6) AND PEPSIN

ACTIVITY (TYROSINE ACTIVITY/ML.) OF GASTRIC

JUICE (NORMAL, 0.5 TO 1)

Date	Six-Hour Periods							
	1		2		3		4	
	Free Acid	Pep-	Free Acid		Free Acid			Pep-
February 17					0.6	2.0	0.9	1.8

shown in Table II. Consistently elevated peptic activity was found, whereas free acid ranged from high values to anacidity. At all times a high degree of digestive activity for the meat bolus was noted. Histamine (0.5 mg.) also was given subcutaneously, and gastric juice was collected twenty, forty and sixty minutes later. Free and total acid contents were found to be slightly elevated after histamine was given.

The twenty-four-hour output of urine catechol amines was 22.5 μ g. by the Henry-Sobel method, with 1.5 μ g./100 ml. of urine as norepinephrine. The same specimen showed a total of 60 μ g./twenty-four hours by Johnson's method (normal: 169 \pm 73). An additional twenty-fourhour specimen (Johnson's method) contained 50.4 μ g.

The tumor was found to contain 92.0 µg. of serotonin per gram of tissue. Urine serotonin was 67, 170, 172, 256 and 336 µg./day in five separate specimens excreted between March and September.

COMMENTS

Since publication of the first recognized descriptions of the carcinoid syndrome [14–16] it has become apparent that the typical manifestations of vasomotor and angiomatous changes in the skin, diarrhea, bronchoconstriction, edema and cardiac lesions frequently are not all present in any one patient [17,18]. None of the manifestations of the syndrome, in fact, may be present in patients with known excessive production of serotonin [17,18], and the syndrome (rarely) may occur in the absence of gross hepatic metastases [19,20].

In the presence of a variegated clinical picture the diagnosis of metastatic carcinoid, especially in the early stages, has been greatly facilitated by use of the 1-nitroso-2-naphthol color reaction for measurement of 5-HIAA in the urine [2]. This reaction subsequently was adapted to a qualitative screening test [21] which is specific for 5-hydroxyindoles, and is said to be positive in all cases of the syndrome [22]. This test was found to give no false positive reactions in over 1,000 patients [23], although it is apparent that certain drugs (e.g., p-hydroxyacetanilide, methocarbamol, mephenesin carbamate may cause confusing colors [24], and phenothiazine and related compounds cause quenching of the reaction [25].

Thorsen has stated that a negative screening test does not in any way disprove a carcinoid tumor, with or without regional metastases [1]. More surprising, however, is the recent report of a case of metastatic carcinoid in which manifestations of the syndrome were temporarily associated with normal urinary 5-HIAA excretion [13]. Mention of an additional case has also been made [26]. The present case is believed to be the first published instance of metastatic carcinoid disease in which the syndrome was present for an extended time and in which urinary 5-HIAA excretion was normal while the serum serotonin levels were distinctly elevated.

Metabolism. Recent studies have clearly shown that alternate routes of serotonin metabolism occur in patients with the carcinoid syndrome, and also in rats, although the major route of metabolism arises from monoamine oxidase activity, giving 5-HIAA. Other urinary metabolites which have been identified include 5-hydroxyindole-aceturic acid, N-acetyl-5-hydroxytryptamine and 5-hydroxytryptamine glucuronide, as well as serotonin itself [27]. Serotonin glucuronide, in another patient with carcinoid, has been found to constitute 30 per cent of the urinary excretion of serotonin, which was 2.1 mg./day [28]. To ascertain if an alternate pathway of metabolism was significant in the present case, a chromatographic study of the urine was made. 5-HIAA, serotonin, Nacetyl serotonin and 5-hydroxyindoleaceturic acid were not identified, but indoleacetic acid and tryptamine, as well as a third unidentified substance reacting with Ehrlich reagent, were found by paper chromatography in three different solvent systems. Of interest is the fact that the urine gave a positive test for urorosein, confirming the presence of indoleacetic acid. This test frequently is positive in the urine of patients with pellagra, but cannot be considered to be specific for nicotinic acid deficiency [29]. The test has been found to be positive in the urine of one

of two other patients with carcinoid syndrome, both of whom had an increased urinary 5-HIAA output. Indoleacetic acid previously has been noted to be present in carcinoid urine [30], and tryptamine is a known normal constituent of human urine [31]. Although indoleacetic acid was not measured quantitatively, its distinct presence, in the absence of 5-HIAA detectable with the Ehrlich reagent on the chromatograms suggested diversion of serotonin to indoleacetic acid in this case. After administration of radioactive serotonin most of the activity after chromatography was found to move with 5-HIAA, showing that exogenous and, by inference, endogenous serotonin followed the usual metabolic pathway. There was no evidence of conjugation and excretion of serotonin as the glucuronide.

A rare variant of the carcinoid syndrome has been described in which the tumor apparently produces 5-hydroxytryptophan, and argentaffin granules are absent in the tumor tissue [32]. In these cases large amounts of serotonin were found in the urine, with greatly elevated urinary histamine, and with total 5-hydroxyindoles which substantially exceeded 5-HIAA output. In our patient the urinary histamine levels were 3.35 and 3.67 μ g./day, (normal, 12 to 41 μ g./ day), and there was no substantial difference between total 5-hydroxyindoles and 5-HIAA excretion. Furthermore, the urinary serotonin output was small, and argentaffin granules were found in the tumor metastases, excluding such a variant as the cause of low urine 5-HIAA. Plasma 5-HIAA also was found to be as low or lower than usual in cases of carcinoid (range, 0.2 to 0.8 µg./ml. plasma) [17], suggesting that glomerular filtration and tubular secretion of 5-HIAA was not impaired.

Diagnosis. Other procedures have been employed which might facilitate diagnosis in instances of normal 5-HIAA excretion, or cases in which the concentration of 5-HIAA was less than 40 mg./L. These include the skin sensitivity test to serotonin [33], the measurement of urinary 5-HIAA after reserpine administration [34], and a tryptophan loading test [18]. The tryptophan loading test in the present case showed no evidence of increased 5-HIAA excretion after 2 gm. of L-tryptophan administered orally, and there was no significant increase in plasma 5-HIAA. The skin test with serotonin creatinine sulfate produced no evidence of erythema or cyanosis. Reserpine was given in an

effort to determine if serotonin release from the tumor and/or from platelets might give even higher levels of serum and/or plasma serotonin, or increased urine 5-HIAA. Although an increase in urinary 5-HIAA has been noted after reserpine administration in dogs [35], and in patients with carcinoid syndrome [34], no increase in urine 5-HIAA was found. (Fig. 1.) A small increase in plasma 5-HIAA was observed twenty-four hours after reserpine was given. (Fig. 2.) Increased serum serotonin occurred immediately after reserpine administration, and serotonin levels did not fall rapidly in the patient's serum. (Fig. 2.) The change in levels in persons with and without carcinoid tumors is being investigated, and preliminary results indicate that distinct differences are noted [28]. It should be emphasized that reserpine administration may be associated with the appearance of duodenal ulcer [36,37], and therefore its use is not without danger in carcinoid patients, in whom an increased incidence of peptic ulcer has been reported [38].

Urinary tryptophan excretion was variable (Table 1), but was substantially less than the mean value of 443 mg./twenty-four hours noted in the patient with intermittently normal 5-HIAA values [13]. The diagnostic value of this procedure is unknown, and its fundamental significance poorly understood, since up to sixty times the normal amount of diversion of dietary tryptophan to 5-hydroxyindoles occurs in carcinoid syndrome [39]. Although the tryptophan method is said to measure 5-hydroxytryptophan also, excessive amounts of 5-hydroxytryptophan apparently were not present in the present case, because of the low level of total 5-hydroxyindole excretion. Heilmeyer and Clotten [13] speculated that serotonin accumulated in their patient with normal 5-HIAA and elevated urinary tryptophan, and was "degraded" to tryptophan and hydroxytryptophan due to de-differentiation of the tumor cells, and loss of oxidative enzymes. Serotonin and 5-hydroxytryptophan levels were not measured in their patient, however, and it has been suggested that their patient in fact represented an atypical case excreting large quantities of 5-hydroxytryptophan [40].

Snow et al. measured urinary 5-HIAA in terms of mg./gm. creatinine and found a range of 1.0 to 6.6 (3.6 \pm 1.3) in forty normal persons [41]. Using this method of expression, the diagnosis would have been apparent in the present

case, and certain other considerations also make this manner of expression desirable [42]. The serum serotonin also was distinctly elevated, and measurement would have substantiated the

diagnosis before operation.

The total magnitude of 5-HIAA excretion, in the absence of an accessory pathway of metabolism or conjugation of serotinin, is the most sensitive index of the total serotonin production by the body [22]. In this case, although the patient was symptomatic, the total serotonin production must be presumed to have been small in comparison to the usual amounts produced by carcinoid tumors. This fact was confirmed by finding relatively small amounts of serotonin in the tumor metastases. Despite total serotonin production which apparently was within the normal range, hyperserotoninemia clearly was demonstrated, suggesting that in early cases, with minimal tumor metastases, measurement of total circulating serotonin may be of more diagnostic value than determination of 5-HIAA excretion. The mechanism of this elevation in the blood is not understood; it may relate to the rate and site of serotonin production in liver metastases, in contrast with release from Kultschitzky cells of the bowel mucosa in the normal person.

Diagnosis in these cases is not merely of academic interest. Aside from the desirability of early resection of metastases, when possible, surgery has been noted by us to provoke severe hypotension in the presence of carcinoid syndrome, and Stacey has reported two deaths after surgical intervention in patients with carcinoid tumors [43]. Furthermore, because of abdominal symptomatology these patients are

likely to be candidates for operation.

Special Studies. Two other studies were of interest in this patient. Gastric secretory studies showed gastric acid to be somewhat elevated (serotonin has been variously noted to stimulate acid gastric secretion sharply, and to produce a less acid juice rich in mucus and pepsin) [44]. No consistent abnormality of acid secretion has been noted in carcinoid syndrome [22]. The elevation of pepsin production in this case, however, was striking and in accord with the observation of Smith et al. that urinary pepsinogen may be increased in some cases, although gastric pepsin production was not determined [30]. Significant in this regard is the fact that in dogs with Heidenhain pouches the administration of reserpine produces increased peptic activity of the gastric juice, concomitant with a marked

fall in serum serotonin [45]. Increased peptic activity suggests that stimulation of pepsin production may lead to the increased incidence of peptic ulceration noted by MacDonald [38], and may relate to the hemorrhagic mucosal lesions in the stomach of rats given large amounts of 5-hydroxytryptophan [46].

Values for urinary catechol amine excretion have been reported in one case of probable carcinoid [47]. The excretion was normal in that patient, but it was reduced in the present case, raising the question of a possible effect of excessive serotonin production on the synthesis, metabolism or excretion of the catechol amines.

Treatment. Medical management directed at antagonizing the effects of excessive production of serotonin has been futile thus far [22]. Cyproheptadine, a new serotonin antagonist, was given to this patient and produced no marked effect on urine 5-HIAA excretion or in the patient's symptoms, as note with other serotonin antagonists. Isolated perfusion of the liver for twenty minutes with 10 mg. of nitrogen mustard also was ineffectual in this case in changing serotonin levels in serum, urine 5-HIAA or symptomatology. At present, surgical removal of metastases, when feasible, the administration of chlorpromazine and supportive therapy are the preferred forms of treatment.

SUMMARY

A case of primary carcinoid tumor of the ileum, with hepatic metastases, attacks of flushing over a three-year period, elevated serum serotonin and normal 5-HIAA in the urine is described. No significant deviation from the usual pathway of serotonin metabolism was demonstrated, suggesting that in certain cases of carcinoid, with comparatively small production of serotonin by the metastases, hyperserotoninemia may be demonstrated before excessive amounts of 5-HIAA are excreted in the urine.

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Papilledema in Chronic Respiratory Acidosis*

Report of a Case, with Studies on the Blood-Cerebrospinal Fluid Barrier for Carbon Dioxide

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Since Cameron [1] first described papilledema in respiratory acidosis in 1933, a score of similar cases have appeared in the English literature. Recently, Conn et al. [2] and Austen and co-workers [3] reported cases of this syndrome with predominant neurologic manifestations. To date, the pathophysiology of papilledema in pulmonary insufficiency is a subject for speculation [1-4].

It is the purpose of this paper to report a case of papilledema and retinopathy associated with respiratory acidosis. Over a three month period serial and simultaneous determinations were made of arterial blood gases and cerebrospinal fluid pH and pCO₂. The resolution of the eyeground changes under appropriate therapy for the underlying pulmonary disease was followed with fundus photographs. These findings were correlated with the progressive changes observed in arterial blood and spinal fluid pH and pCO₂. The data obtained in this patient permit a more complete understanding of the possible pathogenesis of papilledema in respiratory acidosis.

CASE REPORT

S. L., a fifty-five year old white woman, was admitted to the Medical Service of Duke Hospital on September 2, 1959, for investigation of papilledema. The patient was initially seen in the outpatient department because of low back pain. At the time of the examination essentially asymptomatic bilateral papilledema with retinal hemorrhages was discovered, and she was hospitalized for further evaluation. After careful and repetitive questioning the following history was obtained.

As a child, the patient had had frequent infections of

the lower respiratory tract, including whooping cough. At age thirty-six she had bilateral pneumonia and was told afterwards that she had asthma. She had a chronic cough productive of moderate amounts of whitish sputum, which she attributed to smoking approximately one package of cigarettes per day for over forty years. Five years preceding admission she had a single episode of frank hemoptysis. Chest roentgenograms and sputum examination at that time revealed no abnormalities. In the last several years she had been bothered by intermittent wheezing and had been short of breath with such household activities as sweeping and with climbing one flight of stairs. Her symptoms were increased with frequent infections of the respiratory tract and in the year preceding admission she required antibiotic therapy on three occasions. At no time did she have difficulty with mentation, increased somnolence, tremor, peripheral edema or orthopnea. Headaches occurred infrequently, and the only visual disturbance was two transient episodes of gray vision occurring in the two weeks preceding admission. During this period of time she was taking small doses of cortisone derivatives prescribed by her local physician for control of wheezing.

In 1957 the patient was admitted to the Neurosurgical Service for investigation of low back pain which was thought to be secondary to hypertrophic arthritis. On that occasion tortuosity of the retinal veins was noted bilaterally but funduscopic examination was otherwise within normal limits.

On physical examination, temperature was 37.6°c., pulse 94, respiration 22, and blood pressure 125/80 with 15 mm. Hg paradox. The patient was a moderately obese white woman who complained of back pain. She was oriented, and her mental function was intact as tested by serial sevens, general knowledge and recall. There was a moderate dusky discoloration of the mucous membranes. The conjunctivas were suffused. The pupils were regular and reactive with

^{*} From the Department of Medicine, Duke University Medical Center, Durham, North Carolina. This study was supported (in part) by a grant from the American Heart Association and (in part) from the Life Insurance Medical Research Fund.

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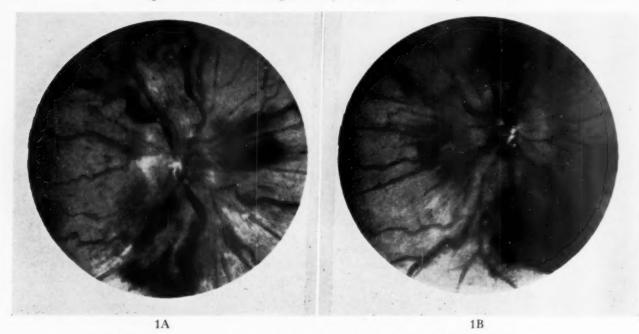


Fig. 1. Eyeground photographs A, right and B, left eye taken on September 10, 1959.

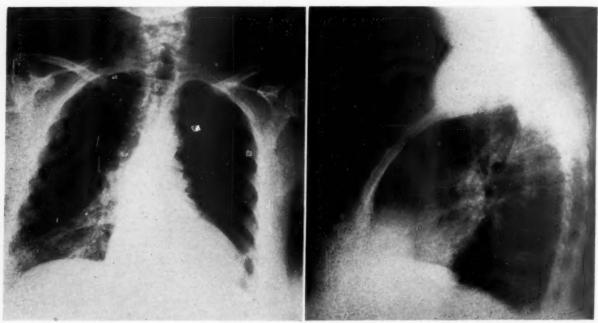


Fig. 2. Posteroanterior and left lateral views of the chest.

normal extraocular movements. Peripheral visual fields were intact but there was minimal enlargement of the central blind spot. Visual acuity was 20/300 o.u. without glasses, and corrected was 20/25 o.d. and 20/30 o.s. The fundi showed florid bilateral papilledema with indistinct disc margins and large fresh hemorrhages clustered around both discs. The retinal veins were engorged and tortuous. (Fig. 1.) The neck was supple and without venous distention. The anteroposterior chest diameter was increased. Breath sounds were distant and inspiratory and expiratory wheezes were heard throughout both lung

fields. There was no physically detectable cardiomegaly. The second pulmonic sound was louder than the second aortic sound. No murmurs or gallops were heard. The liver was not palpable. There was moderate scoliosis of the dorsolumbar spine with tenderness over the right sacroiliac region. The nail beds were dusky but clubbing was absent. There was no peripheral edema. Neurologic examination, except for the finding of papilledema, was within normal limits.

Laboratory data revealed a hemoglobin of 18.5 gm. per cent, a hematocrit of 56 per cent, and a white count of 7,150 per cu. mm. with a normal differential.

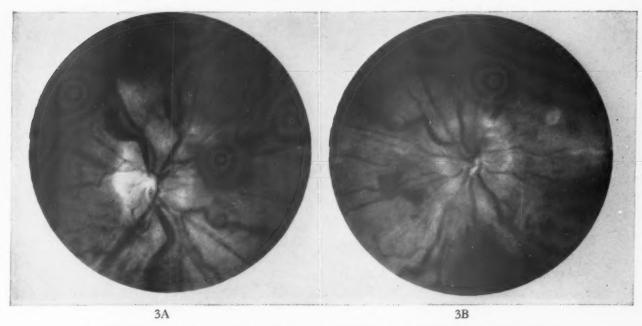


Fig. 3. Eyeground photographs A, right eye and B, left eye taken on September 21, 1959.

Urine pH was 5 and 5.5. CO₂ combining power was 38.5 mEq./L. and other serum electrolytes were within normal limits. Blood urea nitrogen was 9 mg. per cent. The result of a glucose tolerance test was normal. A chest roentgenogram revealed bronchovascular thickening and moderate emphysema. (Fig. 2.) The electrocardiogram showed low voltage in the frontal plane with delayed progression of the QRS complex across the precordium and inverted T waves in leads V1 through V4; the QRS loop was broad and of indeterminate axis. Skull films and electroencephalogram did not show any abnormalities. Urinary excretion of 17-hydroxyketosteroids and 17-ketosteroids was also normal. Venous pressure was 136 mm. of water. A lumbar puncture on September 9 revealed an initial pressure of 200 mm. of water, but the patient was not well relaxed. Five mononuclear cells, 70 mg. per cent of protein, and a negative colloidal gold curve were observed. On September 16 the spinal fluid pressure was 135 mm. of water. Vital capacity and maximum breathing capacity were 84 and 54 per cent of predicted normal. The helium washout time was prolonged to nine minutes. Arterial blood studies revealed oxygen unsaturation, with a pH of 7.25, and a pCO2 of 97.5 mm. Hg. Following six minutes of breathing 5 per cent carbon dioxide in air, the minute volume of ventilation increased 5.85 L. and the tidal volume increased approximately 300 ml.

The patient was treated with nebulized Isuprel® and Alevaire,® using an intermittent positive pressure breathing device. Expectorants and a ten-day course of tetracycline were also administered. On this therapeutic program there was a gradual decrease in wheezing and dyspnea, with simultaneous improvement of the fundi. The disc margins became more distinct, and there was resorption of the hemorrhages. (Fig. 3.)

On the eighth and the fifteenth day of hospitalization simultaneous determinations of arterial blood gases and cerebrospinal fluid pH and pCO₂ were obtained. Blood oxygen content and saturation were measured by the photometric method of Hickam and Frayser [5]. The pH of whole blood was measured with a Cambridge model R pH meter with enclosed glass electrode. Measurements were corrected to

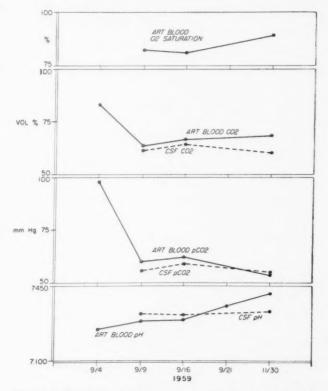


Fig. 4. Serial determinations on arterial blood and spinal fluid.

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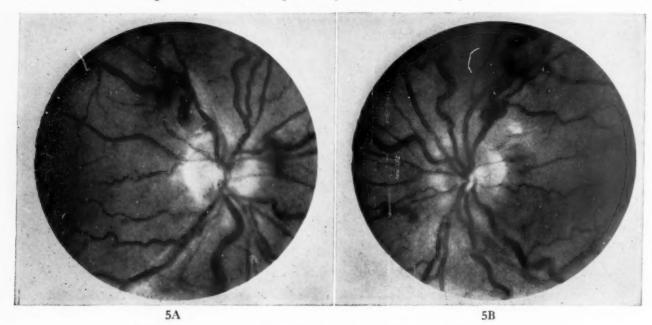


Fig. 5. Eyeground photographs A, right eye and B, left eye taken on November 30, 1959.

37°c. using Rosenthal's factor [6]. Cerebrospinal fluid pH was measured with the same apparatus at room temperature. No temperature correcting factor was applied to these readings, since on four occasions they were found to be comparable (within 0.01 units) to the values obtained at 37°c. on a Cambridge model R pH meter equipped with an anaerobic chamber and a constant temperature bath. Total carbon dioxide content of blood and spinal fluid was determined by the method of Van Slyke and Neill [7]. Plasma carbon dioxide content was calculated from whole blood carbon dioxide content, pH and hemoglobin, using the line chart of Van Slyke and Sendroy [8]. Carbon dioxide tension of blood and cerebro-

TABLE I

ARTERIAL BLOOD-SPINAL FLUID GRADIENTS FOR PH AND PCO₂

Date 1959	Blood	Cerebrospinal Fluid	Difference
		pН	
9/9	7.28	7.32	-0.04
9/16	7.29	7.31	-0.02
11/30	7.41	7.32	+0.09
		pCO ₂ mm. Hg	
9/9	59.7	55.4	+4.3
9/16	62.0	58.9	+3.1
11/30	54.0	54.2	2

spinal fluid was calculated using the Henderson-Hasselbalch equation and a pK' of 6.13 for spinal fluid. All determinations were made in duplicate.

The results obtained are illustrated in Figure 4 and Table 1. The arterial oxygen saturation was 82.9 per cent and remained essentially unchanged (September 9 and 16). A progressive rise in arterial pH with a corresponding fall in pCO₂ was noted. The spinal fluid showed no significant variation in these parameters. The arterial blood-cerebrospinal fluid pH gradient was negative on the two determinations (minus 0.04 and minus 0.02); the corresponding pCO₂ gradients were positive (plus 4 and plus 3 mm. Hg). Just before discharge (September 21) the arterial pH was 7.36.

On November 30 the patient was seen in the outpatient department for follow-up. She had been doing well, except for one episode of bronchopulmonary infection which had responded promptly to antibiotic therapy. On examination of the chest the breath sounds were again distant, and occasional inspiratory rhonchi were heard. The striking improvement of the fundi is shown in Figure 5. Arterial blood showed an oxygen saturation of 89.1 per cent, pH 7.41, and pCO₂ 54 mm. Hg. Spinal fluid obtained simultaneously revealed a pH of 7.32 and a pCO₂ of 54.2 mm. Hg. The arterial-spinal fluid gradients for pH and pCO₂ were now opposite to the ones found on previous determinations, being plus 0.09 for pH and minus 0.2 for pCO₂. (Fig. 4 and Table 1.)

COMMENTS

This case presents several interesting aspects. Although a history of respiratory disease was documented on initial evaluation of the patient, its significance was not appreciated. Her presenting complaint was severe back pain. Dyspnea

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was not noted, but exertion had been limited by the back pain. The pulmonary findings on physical evaluation were not of a magnitude usually associated with respiratory acidosis or with its neurologic complications. Other possibilities considered more likely were brain tumor, particularly of the infratentorial angiomatous type [10], primary polycythemia [11-13], diabetic retinopathy and papillitis. These were excluded by appropriate studies. Papilledema secondary to withdrawal of steroids [14] was also considered unlikely. In retrospect, a more accurate history was obtained when the roentgenograms and the pulmonary function studies indicated the presence of a significant degree of lung disease and the arterial blood gases revealed evidence of respiratory acidosis. Striking and maintained improvement on adequate therapy substantiated the diagnosis. Papilledema in this patient occurred with only modest respiratory symptoms and signs. Arterial blood gas determinations on the day of admission would have delineated the degree of pulmonary insufficiency and clarified the diagnostic difficulties. The importance of this laboratory information in patients with papilledema and any suggestion of lung disease should be emphasized.

Multiple factors have been implicated by various investigators as possible causes of papilledema in respiratory insufficiency [1-4,11, 14-17]. In our patient there was no evidence of congestive heart failure, primary polycythemia or significant elevation of cerebrospinal fluid pressure. She did, however, manifest a marked degree of carbon dioxide retention. There is extensive clinical and experimental evidence in the literature to demonstrate that hypercapnia increases cerebral blood flow and produces edema of the brain [3,15,18-23]. In our patient papilledema was not secondary to increased intracranial pressure which would be expected with diffuse cerebral edema. The mechanism by which metabolic and circulatory derangements result in the eyeground changes is poorly understood. Apparently, hypercapnia and possibly hypoxemia can alter cerebral and retinal metabolism resulting in papilledema and retinopathy.

As far as it can be ascertained, no observations of pH or pCO₂ gradients between spinal fluid and arterial blood have been made in patients with papilledema from respiratory acidosis. General agreement is found in the literature that spinal fluid pH is lower than arterial blood pH, although this difference has not been as yet satisfactorily explained [24–26]. The spinal fluid pH appears to be regulated

primarily by the carbon dioxide tension. It has been shown that this gas diffuses readily across the blood-brain barrier in physiologic as well as in experimental conditions whereas the combined form of carbon dioxide is transferred across the barrier at a much slower rate [25–29]. It would appear that under normal conditions carbon dioxide in the gaseous form flows from brain tissue to cerebral venous blood and cerebrospinal fluid, and hence into the systemic circulation, with a total tension drop of approximately 15 mm. Hg [24,30].

In our patient during the initial period of treatment, when the eyeground changes were still prominent, the arterial blood pH was persistently lower and the pCO₂ higher than the respective spinal fluid values. These findings must be considered as actual reversion of the normal gradients, since the pH and pCO₂ differences are definitely outside the limits of error expected for the methods used in the respective determinations. When the respiratory insufficiency was corrected, the eyeground lesions regressed, and at this time both gradients were reversed toward normal directions, i.e., pH lower and pCO₂ higher in cerebrospinal fluid than in arterial blood.

With pulmonary insufficiency and attendant arterial carbon dioxide retention, the normally existing spinal fluid-arterial blood pCO2 gradient may be reversed. Brain tissue is capable of absorbing large quantities of carbon dioxide [31]. The reversed gradient may therefore persist over a long period of time, until a saturation point is reached in the brain tissue or until arterial hypercapnia is corrected by improving the pulmonary function. The toxic effect of carbon dioxide accumulation within the brain substance may be responsible for local vasodilation, increased cerebral blood flow, increased vascular permeability, and possibly altered cell metabolism resulting in papilledema and retinopathy. Since in this patient arterial oxygen saturation returned toward normal values concomitantly with the progressive correction of hypercapnia, the role of hypoxemia in the pathogenesis of papilledema from respiratory acidosis cannot be defined.

SUMMARY

A case of papilledema and retinopathy associated with pulmonary insufficiency in a fifty-five year old woman with chronic bronchitis and emphysema is reported. This presentation exemplifies the diagnostic difficulties encountered in identifying the underlying disorder in

cases of papilledema and retinopathy secondary to lung disease, since the pulmonary symptoms of this patient, as well as her chest findings on physical examination and roentgenograms, were

not prominent.

Repeated studies were made of arterial blood gases and cerebrospinal fluid pH and pCO₂ during a three month period. The progressive resolution of the eyeground lesions was correlated with improved respiratory function. Hypercapnia and hypoxemia have been suspected as the cause of papilledema in respiratory acidosis. The results of this study suggest that in respiratory acidosis accumulation of carbon dioxide in brain tissue, as reflected by inversion of the normal carbon dioxide tension gradient between cerebrospinal fluid and arterial blood, may be related to the development of papilledema and retinopathy.

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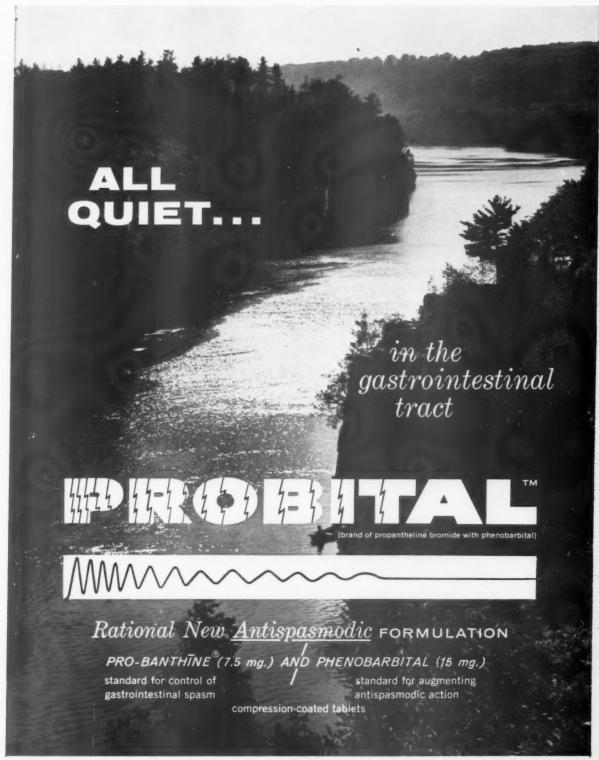
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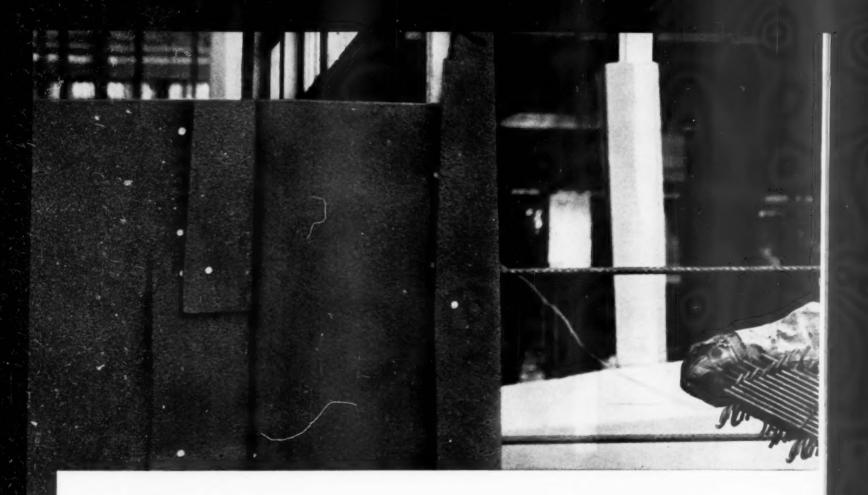
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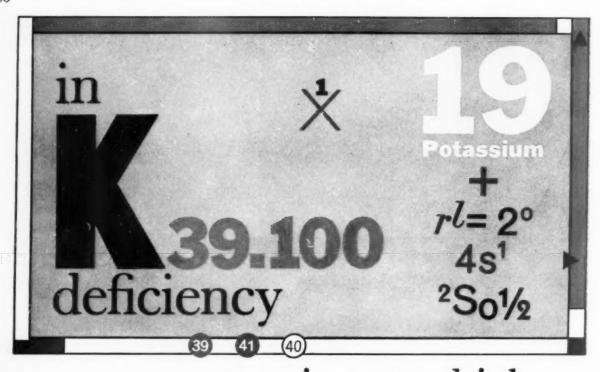
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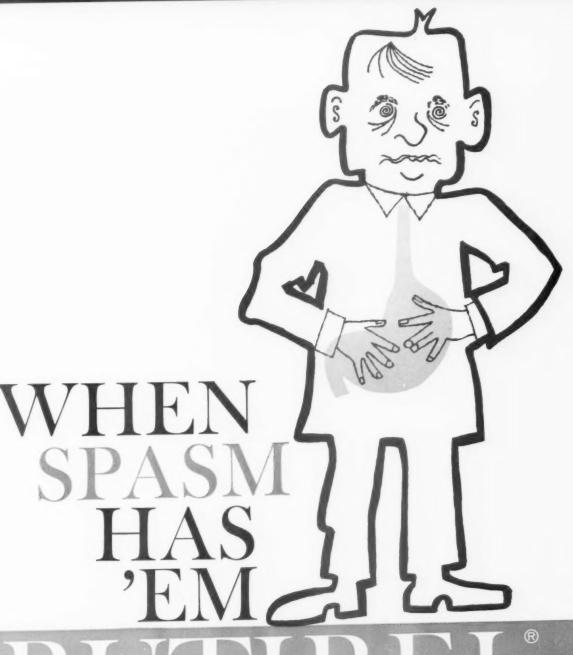
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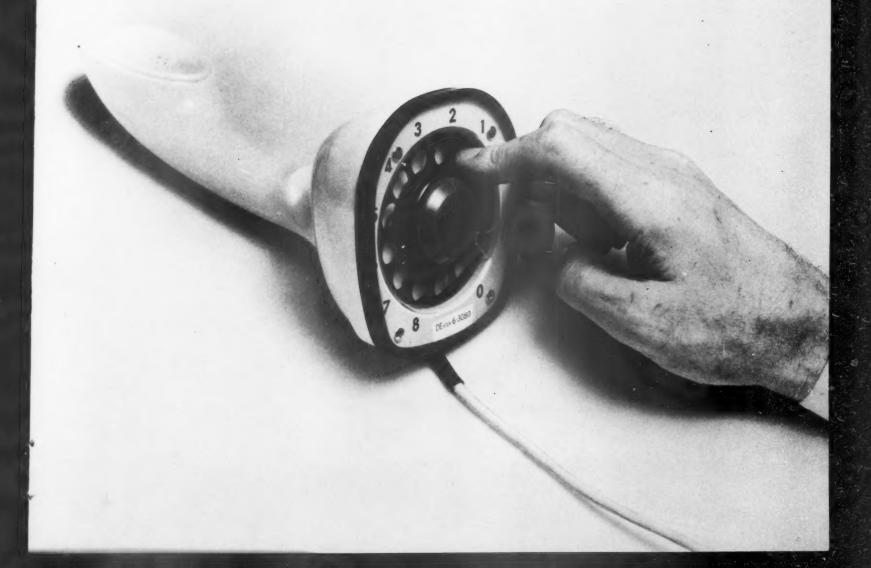
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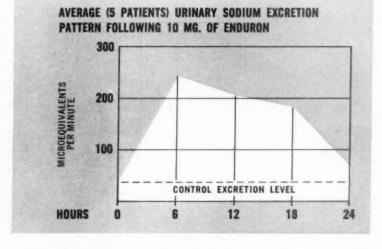
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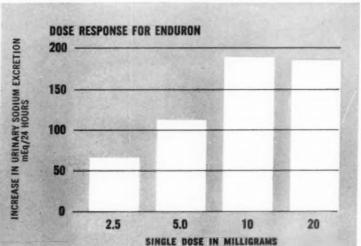
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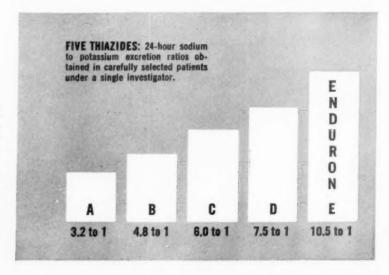
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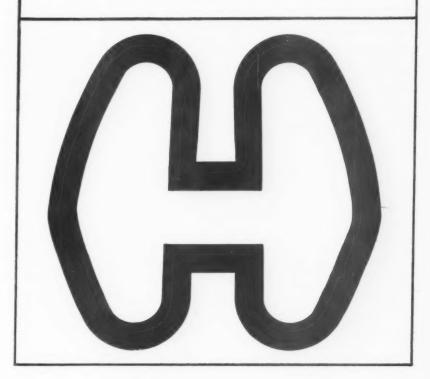
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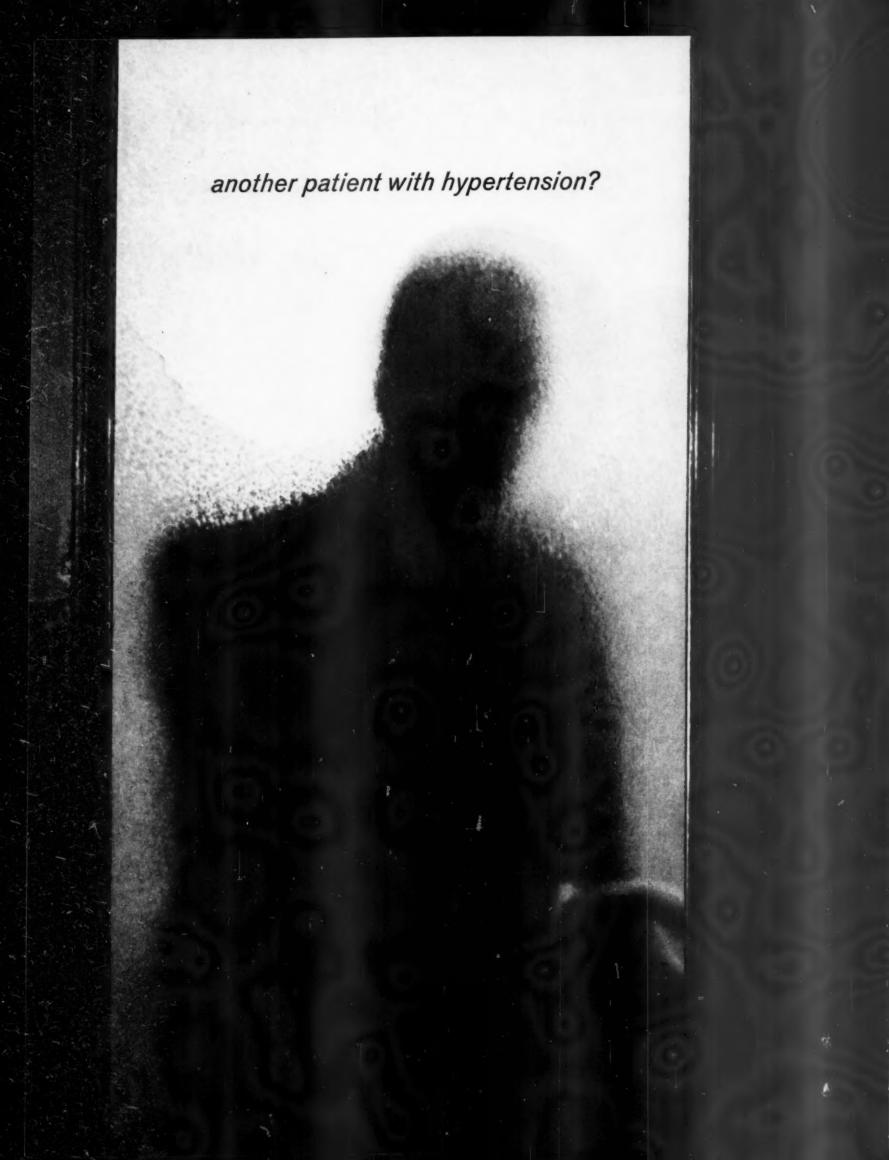
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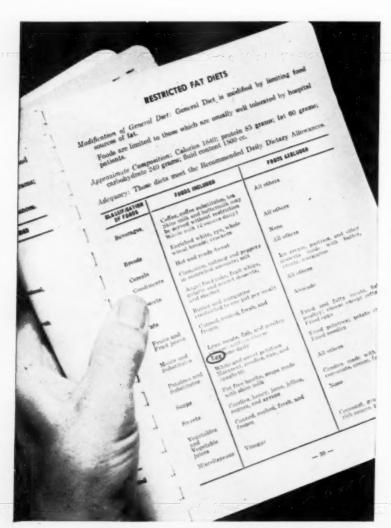
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The page here reproduced appears in the Diet Manual of the hospitals associated with Northwestern University Medical School, a distinguished teaching center.



In diet manuals of medical teaching centers throughout the United States eggs are included in restricted fat diets.

This suggestion is based on the high overall nutritional value of eggs. The quality of egg protein is a standard against which other food protein is measured. The ratio of saturated to unsaturated fatty acids in egg yolk is in keeping with present-day thinking on this subject. The vitamin-mineral content supplies essentials for daily needs.

Eggs, one of the best sources of needed nutrients, fit into virtually every diet, including restricted fat, low sodium, low fiber, many other restricted diets, and of course the normal diet for all ages.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.



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Sleep is sorcery...enchanted healer of care. And non-barbiturate Placidyl is the wand that subtly summons it. Placidyl casts a spell both prompt and effective...then lifts it, without hangover, on a refreshed new morning. No magic required to grant slumber to the restive. Just...sssh!...Placidyl.





Placidyl® nudges your patient to sleep





Geriactive with Gerilets

Leisuretime, of course, needn't mean a hyperabundance of activity. However, whatever the interests of your geriatric patient, you'll naturally do everything you can to help make his existence more meaningful.

And, in prescribing Filmtab Gerilets, you're giving the older patient the kind of dietary and therapeutic support which often may contribute to a more productive life.

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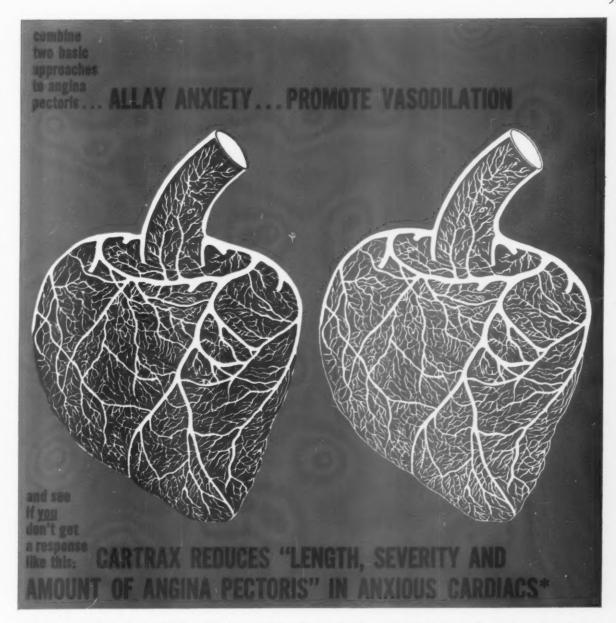
formula, you'd find these components featured:

B-Complex and Oil-Soluble Vitamins . . . Hematopoietic Factors . . . Lipotropic Factors ... Hormones ... Anti-Depressant and Capillary Stability Factors.

An added advantage, appreciated in particular by the finicky patient, is Gerilets'exclusive Filmtab coating. Makes for a streamlined tablet. Also makes it that much easier to stay "Geriactive with Gerilets."

STREAMLINED INTO THE SMALLEST TABLET DO OF ITS KIND





Clark treated 31 anginal patients who showed signs of anxiety, fear, excitement and other forms of emotional stress. On CARTRAX, all 31 fared better than they had on previous therapy . . . as judged both by subjective reports and by reduced nitroglycerin requirements.*

CARTRAX combines PETN (for prolonged vasodilation) with ATARAX (the tranquilizer preferred for angina patients because of its safety and mild antiarrhythmic properties). Thus, CARTRAX helps you to cope with both components of angina pectoris-circulatory and emotional.

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*Clark, T. E., in press.

PETN+ATARAX **110" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. For dosage flexibility, CARTRAX **20" (pink) tablets (20 mg. PETN plus 10 mg. ATARAX) may be utilized at a level of one tablet three to four times a day. The tablets should be administered before meals for optimal response. For convenience, write "CARTRAX 10" or "CARTRAX 20." As with all nitrates, use with caution in glaucoma. Supplied: In bottles of 100. Prescription only.



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† pentaerythritol tetranitrate †† brand of hydroxyzine

Just Released

a Symposium on new methods of diagnosis and management of

Peptic Ulcer

Here is an outline of the contents:

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THE AMERICAN JOURNAL OF MEDICINE

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a new, improved, more potent relaxant for anxiety and tension

- · effective in half the dosage required with meprobamate
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 - neither depression nor significant toxicity has been reported



- · a familiar spectrum of antianxiety and muscle-relaxant activity
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- · no cumulative effect
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STRIATRAN is indicated in anxiety and tension, occurring alone or in association with a variety of clinical conditions.

Adult Dosage: One tablet three times daily, preferably just before meals. In insomnia due to emotional tension, an additional tablet at bedtime usually affords sufficient relaxation to permit natural sleep.

Supply: 200 mg. tablets, coated pink, bottles of 100.

While no absolute contraindications have been found for Striatran in full recommended dosage, the usual precautions and observations for new drugs are advised.

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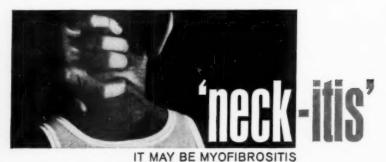
in any rheumatic 'itis'





IT MAY BE EARLY RHEUMATOID ARTHRITIS





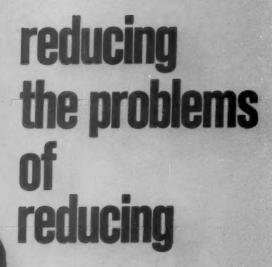


The favored corticoid-salicylate compound. For more effective and comprehensive, yet conservative, treatment than either steroids or salicylates alone... the outstanding anti-inflammatory effect of prednisone¹... the supportive antirheumatic action of aspirin^{2,3}. to bring rapid pain relief and quiet the inflammatory process. SIGMAGEN offers less likelihood of treatment-terminating side effects.² SIGMAGEN is available in bottles of 100 and 1000.

References: 1. Cohen, A., et al.: <u>J.A.M.A.</u> 165:225, 1957. 2. Spies, T. D., et al.: <u>J.A.M.A.</u> 159:645, 1955. 3. Stecher, R. M.: <u>Panel Discussion</u>, Ohio M. J. 52:1037, 1956.

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Sigmagen



Preludin

Tablets and Endurets®

an oxazine...
not an amphetamine

Unsurpassed Effectiveness

In all controlled clinical studies, Preludin has produced impressively greater weight loss than placebo tablets regardless of the degree of enforcement of dietary restriction.

Exceptionally High Tolerance

Reports are numerous of successful use of Preludin in cases intolerant of other anorexiants.

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Available as scored tablets of 25 mg. for b.i.d. or t.i.d. administration and also as Endurets[®], 75 mg., for once daily administration



Geigy Pharmaceuticals
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Precautions and Contraindications

Although there have been no reports of

Preludin®, brand of phenmetrazine hydrochloride.

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significant toxic reactions to Preludin, on theoretical grounds it should not be given to patients with severe hypertension, thyrotoxicosis or acute coronary disease. Preludin may be used with caution in cases of moderate hypertension

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Inflammatory reaction following stress!

In inflammation, either localized or generalized in nature, capillary damage — increased permeability, resulting in seepage of blood constituents into the tissues — is a uniform basic reaction resulting from injury or stressors of various types:

7

PHYSICAL: Trauma, surgery, overexertion, sprains

NUTRITIONAL: Malnutrition, toxins, pregnancy, growth

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DISEASE STATES: Viral, bacterial, malignancies, endocrine

The role of the citrus bioflavonoids in the prevention or reversal of the inflammatory process is multiple through:

- 1. Maintenance of capillary integrity
- 2. In cellular metabolic processes, by potentiating corticosteroids, vitamins and essential nutrients, and by inhibition of hyaluronidase
- 3. Direct anti-inflammatory action

In the treatment of inflammatory conditions include the citrus bioflavonoids (Lemon Bioflavonoid Complex, Hesperidin Complex and Hesperidin Methyl Chalcone) as therapeutic adjuncts.



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cough sedative | antihistamine decongestant | expectorant

■ relieves cough and associated symptoms in 15-20 minutes ■ effective for 6 hours or longer ■ promotes expectoration ■ rarely constipates ■ agreeably cherry-flavored

Each teaspoonful (5 cc.) of Hycomine* Syrup contains:

Dihydrocodeinone Bitartrate (Warning: May be habit-forming) Homatropine Methylbromide 6.5 mg. 12.5 mg. 10 mg. 60 mg.

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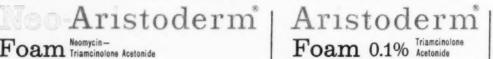
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7.5 cc. and 15 cc. push-button dispensers Neat, not messy or stickyspreads readily without irritation or burning—for oozing, crusted, severely inflamed and injured skin or mucous membranes.

Each cc. contains: Aristocort Triamcinolone Acetonide, 1 mg. . . . 0.1% Neomycin Sulfate, 5 mg. 0.5%

Precautions: Contraindicated in herpes simplex. Sensitivity reactions to neomycin occasionally occur.



7.5 cc. push-button dispenser



Precautions: Contraindicated in herpes simplex

Aristocort

Cream 0.1% Triamcinolone Acetonide

Tubes of 5 and 15 Gm.



Precautions: Contraindicated in herpes simplex. and allergic skin conditions . . . simple, sparing application — prompt, symptomatic relief —

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The anti-inflammatory and antipruritic efficacy of triamcinolone acetonide was shown by the prompt control of itching and resolution of affected areas. Cahn, M. M., and Levy, E. J.: A Comparison of Topical Corticosteroids: Triamcinolone Acetonide, Prednisolone, Fluorometholone, and Hydrocortisone.

Antibiotic Med. & Clin. Ther. 6:734 [Dec.] 1959.

Aristocort Ointment 0.1% Triamcinolone Acetonide

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Tubes of 1/8 oz.

For inflammatory, allergic, infective eye and ear conditions

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muscle spasm, nervous tension

rapid action · non-narcotic · economical

"We have found caffeine, used in combination with acetylsalicylic acid, acetophenetidin, and isobutylallylbarbituric acid, [Fiorinal] to be one of the most effective medicaments for the symptomatic treatment of headache due to tension." Friedman, A. P., and Merritt, H. H.: J.A.M.A. 163:1111 (Mar. 30) 1957.

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Dosage: 1 or 2 every four hours, according to need, up to 6 per day.



Many **MIGRAINE** attacks can be **stopped at the start** by the prompt use of...

'MIGRAL'®

Advantage

'MIGRAL' permits maximum ergotamine therapy with the first dose
—because the 'MIGRAL' formula includes the proved antiemetic,
cyclizine hydrochloride, to counteract the tendency to nausea and
vomiting.

Dosage

'MIGRAL' should be taken immediately at the start of a migraine attack, and the effective dosage should be determined on an individual basis. When the total dosage necessary to stop an attack has been determined, that amount should be taken as initial dosage in subsequent attacks.

In general, 2 to 4 'MIGRAL' tablets taken at the first sign of an attack will terminate a headache by preventing progression to the vasodilation stage. If treatment is not started sufficiently early to achieve this result, an additional 1 or 2 tablets should be administered every half hour until the patient is relieved, or until a total dosage of 6 tablets has been taken.

Caution

It is recommended that not more than 6 tablets be taken during a single attack, nor more than 10 tablets per week.



BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York







UPJOHN ANNOUNCES



Didrex







in obesity management Put it to your patient this

PERSISTENT WEIGHT LOSS

WEEK AFTER WEEK

way: The basic therapeutic objective of obesity management is to change dietary habits built over

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BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride $\lfloor (+)\text{-N-benzyl-N},\alpha\text{-dimethyl-phenethylamine hydrochloridel}. A sympathomimetic compound with marked anorexic action and relatively little stimulating effect on the CNS or cardiovascular system.$

Indications: Control of obesity.

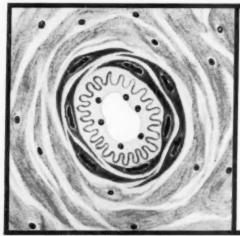
Contraindications: None known. However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

Dosage: Initiate appetite control with $\frac{1}{2}$ or 1 tablet (25 to 50 mg.) in midmorning for several days. Then adjust dosage to suit each patient's need to a maximum of 3 tablets daily (150 mg.). Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 50 mg., press-coated, scored tablets, in bottles of 100.

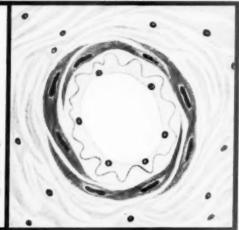
Why combining Esidrix[®] with Serpasil* improves control of high blood pressure

The presence of excess tissue fluids and salt can keep constricted blood vessels from dilating fully in response to antihypertensive drugs. ■ This may explain why the antihypertensive effect of Serpasil-Esidrix is better than average. By depleting fluid and electrolytes from surrounding tissue, Esidrix enables blood vessels to dilate to physiologic limits. Result: Peripheral resistance is reduced and blood pressure goes down - often to lower levels than can be achieved with single-drug therapy. Complete information sent on request.



Schematic diagram illustrates constrictive effect of fluids and salt on vascular wall.

> Esidrix depletes fluid and salt, increases ability of vessel to respond to Serpasil.



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potent antihistaminic—relieves nasal stuffiness, sneezing, lacrimation, itching, and bronchial congestion

proved expectorants—liquefy and loosen tenacious mucus. , help clear the respiratory tree time-tested antisparmodic—decreases bronchosnasm: helps quiet the cough reflex

palatable demulcent - raspberr & flavored syrup soothes raw, irritated throat membranes ... pleasant taste is readily acceptable to patients of all ages

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Created especially for those patients whose emotional condition complicates the treatment of hypertension and congestive failure

Now the most widely prescribed diuretic-antihypertensive, hydrochlorothiazide, is combined with the most widely prescribed tranquilizer, meprobamate. Called "Miluretic", it constitutes new, effective therapy for hypertension and congestive failure—especially when emotional factors complicate your treatment.

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Available at all pharmacies Composition: 200 mg. Miltown (meprobamate, Wallace) + 25 mg. hydrochlorothiazide

Dosage: For hypertension, 1 tablet four times a day. For congestive failure, 2 tablets four times a day.

Supplied: Bottles of 50 white, scored tablets

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- · Lessens rigidity and tremor
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- · An effective euphoriant
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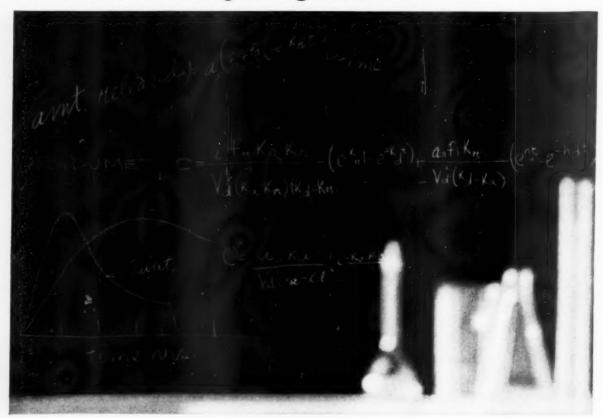
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in obesity, in psychosomatic complaints

1+1=1 DESBUTAL GRADUMET



When severe pain accompanies skeletal muscle spasm ease both 'pain & spasm'



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ROBAXIN® with Aspirin

A dual-acting skeletal muscle relaxant-analgesic, combining the clinically proven relaxant action of ROBAXIN with the time-tested pain relieving action of aspirin.

Each ROBAXISAL Tablet contains:

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SUPPLY: Syrup in bottles of 4 oz, 16 oz, 1 gal. Tablets in bottles of 20, 100, 500. Expectorant in bottles of 16 oz, 1 gal.

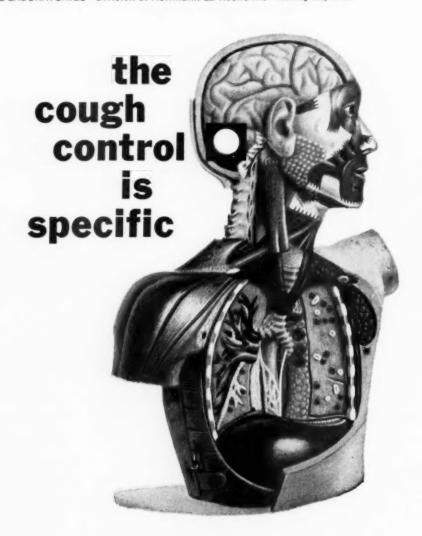
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1. A.M.A. Council on Drugs: New and Nonofficial Drugs 1960, Philadelphia, J. B. Lippincott Company, 1960, p. 363.

2. Friend, D. G., and Hamlin, J. T. III: in Modell, W.: Drugs of Choice 1960-1961, St. Louis, The C. V. Mosby Company, 1960, pp. 270-271.

3. Batterman, R. C., et al.: Clinical Re-evaluation of Daytime Sedatives, Postgrad. Med. 26:502-509 (Oct.) 1959.

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such as that of cancer, characteristically is intensified by fear and anxiety. You can alleviate these emotional reactions that intensify pain and help keep your patient from dwelling on his disease with

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January, 1961

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* Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA.

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Thorazine*	120	Quinaglute*

* Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA.

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MODERIL, a purified alkaloid of ranwolfia, usually lessens the frequency and/or severity of mental depression, sedation, nightmares, gastrointestinal reactions, and other reserpine side effects. Thus, MODERIL adds new significance to the concept that ranwolfia 'should be the first (hypotensive) drug tried and the last omitted.''

1. Meilman, E.; Circulation 13:596, 1956

IN BRIEF

MODERIL is rescinnamine, a purified rauwolfia alkaloid useful in the gradual sustained lowering of blood pressure in mild to moderate labile hypertension. When MODERIL is given with other antihypertensive agents, the latter may often be administered in lower dosage with fewer undesired reactions.

INDICATIONS: Primary therapy in mild to moderate labile hypertension. In more severe cases, as adjunctive therapy with other agents.

ADMINISTRATION AND DOSAGE: Adjust dosage to minimum level for optimal therapeutic effect. Recommended initial dose—one 0.5 mg. tablet twice a day for two weeks. Significant side effects are unusual with MODERIL, but should they occur, reduce dosage to one 0.25 mg. tablet twice daily. When optimal hypotensive effects are obtained during initial period, this same reduced dosage or less may be used. If greater hypotensive effects than those observed during this period are required, cautiously increase dose by 0.25 mg. per day (up to 2.0 mg. per day) and consider combined therapy. Doses should be taken after meals to minimize possible adverse effects of increased gastric secretion.

Initial dosage for children 3-12 years of age is up to 0.25 mg. twice daily for one week. Children should be observed closely and when therapeutic effect is achieved, this dose should be reduced by half, i.e., 0.25 mg. daily.

SIDE EFFECTS: Same type as with reserpine but usually with reduced incidence or severity, e.g., mental depression, bradycardia, nightmares, and fatigue. Nasal stuffiness or congestion may occur but usually disappears with discontinuation of the drug or on use of topical vasoconstrictors or antihistamines. Increased frequency of defecation and/or looseness of stools is an occasional reaction. There have been occasional reports of serious hypotension in persons on rauwolfia compounds who undergo surgery with general or spinal anesthesia. It is suggested that MODERIL be discontinued two weeks before surgery, when feasible, or other appropriate measures be taken.

PRECAUTIONS: Because rauwolfia preparations may increase gastric secretion, MODERIL should be used with caution in patients with a history of peptic ulcer.

SUPPLIED: Yellow, scored, oval tablets of 0.25 mg., bottles of 100 and 500; salmon, scored, oval tablets of 0.5 mg., bottles of 100.

More detailed professional information available on request.

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in long-term administration, as in Arthritis, when aspirin combined with an antacid is desired:

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To prevent or minimize gastric distress which often accompanies prolonged or high level administration of acetylsalicylic acid, ASCRIPTIN provides aspirin in combination with MAALOX®, the preferred professional antacid. The recognized superiority of MAALOX makes ASCRIPTIN a superior aspirin-antacid, with the virtues of buffered aspirin and with the added distinction of being promoted professionally only.

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Supplied: Bottles of 100 and 500 tablets. For severe pain — Capsules ASCRIPTIN with Codeine (codeine phosphate 15 mg.), bottles of 50.



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as powerful as the narcotics in cough suppression... but much longer acting

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one teaspoonful affords 4 to 8 hours' freedom from cough distress ULO maintains its maximal cough-suppressant effect undiminished for 4 to 8 hours, thus calling for fewer daytime doses and usually providing freedom from cough distress through the night.

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Write for Physicians' Reference Brochure with full bibliography.

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Exceptionally well tolerated; no narcotic overlay; compatible with other indicated medications.



Northridge, California

Not all, but almost all allergic patients respond to the basic antihistamine Pyribenzamine

Among these 5 cases, for example...



Miss J. W. responds to Pyribenzamine

Miss W. has had hay fever for 20 years. Condition is most severe in August. One Pyribenzamine Tablet t.i.d. during allergic episodes brings marked improvement — no side effects.



Mr. D. L. responds to Pyribenzamine

Symptoms of seasonal allergic rhinitis persisted in Mr. L. despite treatment with an antihistamine-decongestant spray and an oral antihistamine. Desensitization brought only moderate besensitization brought only moderate relief. On one Pyribenzamine Lontab b.i.d., Mr. L. did very well and was completely



Mrs. D. E. responds to Pyribenzamine

When Mrs. E.'s allergic rhinitis failed to respond to other long-acting antihistamines, her physician prescribed Pyribenzamine Lontabs. Result: Sneezing, tearing and nasal congestion "just about disappeared,"



Miss T. E. does not respond to Pyribenzamine

Miss E. has allergic Miss E. has allergic symptoms (itching of eyes, skin irritation, nasal congestion) throughout the year with hay fever in August and September. Physician reports Pyribenzamine not effective; patient now takes diphenhydramine hydrochloride.



Mrs. B. R. responds to Pyribenzamine

Rose fever and hay fever plagued Mrs. R. Her physician reports therapy with Pyribenzamine "extremely successful." Mrs. R. states that after taking the drug "everything is fine in about 20 minutes."

